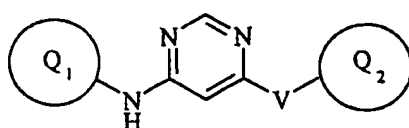
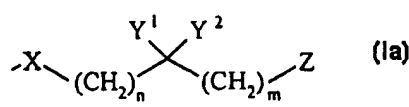


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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : C07D 239/46, A61K 31/505, A61P 35/00	A1	(11) International Publication Number: WO 00/59892 (43) International Publication Date: 12 October 2000 (12.10.00)
(21) International Application Number: PCT/GB00/01258 (22) International Filing Date: 3 April 2000 (03.04.00) (30) Priority Data: 9907658.0 6 April 1999 (06.04.99) GB (71) Applicant (for all designated States except US): AS-TRAZENECA AB [SE/SE]; S-151 85 Södertälje (SE). (72) Inventors; and (75) Inventors/Applicants (for US only): BREAUULT, Gloria, Anne [US/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). JAMES, Stewart, Russell [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). PEASE, Janet, Elizabeth [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). (74) Agent: BRYANT, Tracey; Astrazeneca, Global Intellectual Property, P.O. Box 272, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4GR (GB).		(81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: PYRIMIDINE COMPOUNDS WITH PHARMACEUTICAL ACTIVITY		
<div style="display: flex; align-items: center; justify-content: space-around;"> <div style="text-align: center;">  <p>(I)</p> </div> <div style="text-align: center;">  <p>(Ia)</p> </div> </div>		
(57) Abstract <p>A pyrimidine derivative of formula (I) wherein V is O or S, Q₁ and Q₂ are independently selected from phenyl, naphthyl, a 5- or 6-membered monocyclic moiety and a 9- or 10-membered bicyclic heterocyclic moiety; and Q₁ is substituted by one substituent of formula (Ia), and Q₂ may optionally bear further substituents of formula (Ia) wherein X is CH₂-, O-, NH-, NR^y- or -S- [wherein R^y is as defined within]; Y¹ is H, C₁₋₄alkyl or as defined for Z; Y² is H or C₁₋₄alkyl; Z is R^aO-, R^bR^cN-, R^dS-, R^eR^fNNR^g-, a nitrogen linked heteroaryl or a nitrogen linked heterocycle, wherein R^a, R^b, R^c, R^d, R^e, R^f and R^g are as defined within; n is 1, 2 or 3; m is 1, 2 or 3; and Q₁ and Q₂ may optionally be further substituted; or a pharmaceutically acceptable salt or <i>in vivo</i> hydrolysable ester thereof; are useful as anti-cancer agents; and processes for their manufacture and pharmaceutical compositions containing them are described.</p>		

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PYRIMIDINE COMPOUNDS WITH PHARMACEUTICAL ACTIVITY

The invention relates to pyrimidine derivatives, or pharmaceutically acceptable salts or *in vivo* hydrolysable esters thereof, which possess cell-cycle inhibitory activity and are
5 accordingly useful for their anti-cell-proliferation (such as anti-cancer) activity and are therefore useful in methods of treatment of the human or animal body. The invention also relates to processes for the manufacture of said pyrimidine derivatives, to pharmaceutical compositions containing them and to their use in the manufacture of medicaments of use in the production of an anti-cell-proliferation effect in a warm-blooded animal such as man.

10 A family of intracellular proteins called cyclins play a central role in the cell cycle. The synthesis and degradation of cyclins is tightly controlled such that their level of expression fluctuates during the cell cycle. Cyclins bind to cyclin-dependent serine/threonine kinases (CDKs) and this association is essential for CDK (such as CDK1, CDK2, CDK4 and/or CDK6) activity within the cell. Although the precise details of how each of these
15 factors combine to regulate CDK activity is poorly understood, the balance between the two dictates whether or not the cell will progress through the cell cycle.

The recent convergence of oncogene and tumour suppressor gene research has identified regulation of entry into the cell cycle as a key control point of mitogenesis in tumours. Moreover, CDKs appear to be downstream of a number of oncogene signalling
20 pathways. Disregulation of CDK activity by upregulation of cyclins and/or deletion of endogenous inhibitors appears to be an important axis between mitogenic signalling pathways and proliferation of tumour cells.

Accordingly it has been recognised that an inhibitor of cell cycle kinases, particularly inhibitors of CDK2, CDK4 and/or CDK6 (which operate at the S-phase, G1-S and G1-S phase
25 respectively) should be of value as a selective inhibitor of cell proliferation, such as growth of mammalian cancer cells.

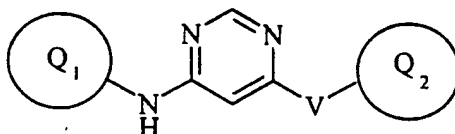
The present invention is based on the discovery that certain pyrimidine compounds surprisingly inhibit the effects of cell cycle kinases, particularly CDK2, CDK4 and CDK6, and thus possess anti-cell-proliferation properties. Such properties are expected to be of value
30 in the treatment of disease states associated with aberrant cell cycles and cell proliferation such as cancers (solid tumours and leukemias), fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic

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nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation.

According to the invention there is provided a pyrimidine derivative of the formula

(I):

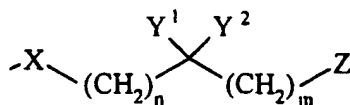


(I)

wherein

V is O or S;

Q₁ and Q₂ are independently selected from phenyl, naphthyl, a 5- or 6-membered monocyclic moiety (linked via a ring carbon atom and containing one to three heteroatoms independently selected from nitrogen, oxygen and sulphur); and a 9- or 10-membered bicyclic heterocyclic moiety (linked via a ring carbon atom and containing one or two nitrogen heteroatoms and optionally containing a further one or two heteroatoms selected from nitrogen, oxygen and sulphur); provided that there is an available carbon atom in Q₁ such that the substituent of formula (Ia) (defined hereinbelow) is not adjacent to the -NH-link; and Q₁ is substituted on an available carbon atom not adjacent to the -NH-link one substituent of the formula (Ia), and Q₂ may optionally bear on any available carbon atom further substituents of the formula (Ia):



(Ia)

wherein:

X is -CH₂-, -O-, -NH-, -NR^y- or -S- [wherein R^y is C₁₋₄alkyl, optionally substituted by one substituent selected from halo, amino, cyano, C₁₋₄alkoxy or hydroxy];

Y¹ is H, C₁₋₄alkyl or as defined for Z;

Y² is H or C₁₋₄alkyl;

Z is R^aO-, R^bR^cN-, R^dS-, R^eR^fNNR^g-, a nitrogen linked heteroaryl or a nitrogen linked heterocycle [wherein said heterocycle is optionally substituted on a ring carbon or a ring nitrogen by C₁₋₄alkyl or C₁₋₄alkanoyl] wherein R^a, R^b, R^c, R^d, R^e, R^f and R^g are independently

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selected from hydrogen, C₁₋₄alkyl, C₂₋₄alkenyl, C₃₋₈cycloalkyl, and wherein said C₁₋₄alkyl and C₂₋₄alkenyl are optionally substituted by one or more phenyl;

n is 1, 2 or 3;

m is 1, 2 or 3;

- 5 and Q₁ and Q₂ may optionally and independently bear on any available carbon atom up to four substituents independently selected from halo, hydroxy, thio, nitro, carboxy, cyano, C₂₋₄alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent], C₂₋₄alkynyl, C₁₋₅alkanoyl, C₁₋₄alkoxycarbonyl, C₁₋₆alkyl, hydroxy-C₁₋₃alkyl, fluoro-C₁₋₄alkyl, amino-C₁₋₃alkyl, C₁₋₄alkylamino-C₁₋₃alkyl, *N,N*-di-(C₁₋₄alkyl)amino-C₁₋₃alkyl, 10 cyano-C₁₋₄alkyl, C₂₋₄alkanoyloxy-C₁₋₄alkyl, C₁₋₄alkoxy-C₁₋₃alkyl, carboxy-C₁₋₄alkyl, C₁₋₄alkoxycarbonyl-C₁₋₄alkyl, carbamoyl-C₁₋₄alkyl, *N*-C₁₋₄alkylcarbamoyl-C₁₋₄alkyl, *N,N*-di-(C₁₋₄alkyl)-carbamoyl-C₁₋₄alkyl, pyrrolidin-1-yl-C₁₋₃alkyl, piperidin-1-yl-C₁₋₃alkyl, piperazin-1-yl-C₁₋₃alkyl, morpholino-C₁₋₃alkyl, thiomorpholino-C₁₋₃alkyl, piperazin-1-yl, morpholino, thiomorpholino, C₁₋₄alkoxy, cyano-C₁₋₄alkoxy, carbamoyl-C₁₋₄alkoxy, 15 *N*-C₁₋₄alkylcarbamoyl-C₁₋₄alkoxy, *N,N*-di-(C₁₋₄alkyl)-carbamoyl-C₁₋₄alkoxy, 2-aminoethoxy, 2-C₁₋₄alkylaminoethoxy, 2-*N,N*-di-(C₁₋₄alkyl)aminoethoxy, C₁₋₄alkoxycarbonyl-C₁₋₄alkoxy, halo-C₁₋₄alkoxy, 2-hydroxyethoxy, C₂₋₄alkanoyloxy-C₂₋₄alkoxy, 2-C₁₋₄alkoxyethoxy, carboxy-C₁₋₄alkoxy, C₃₋₅alkenyloxy, C₃₋₅alkynyloxy, C₁₋₄alkylthio, C₁₋₄alkylsulphinyl, C₁₋₄alkylsulphonyl, ureido (H₂N-CO-NH-), C₁₋₄alkylNH-CO-NH-, 20 *N,N*-di-(C₁₋₄alkyl)N-CO-NH-, C₁₋₄alkylNH-CO-N(C₁₋₄alkyl)-, *N,N*-di-(C₁₋₄alkyl)N-CO-N(C₁₋₄alkyl)-, carbamoyl, *N*-(C₁₋₄alkyl)carbamoyl, *N,N*-di-(C₁₋₄alkyl)carbamoyl, amino, C₁₋₄alkylamino, *N,N*-di-(C₁₋₄alkyl)amino, C₂₋₄alkanoylamino,

- and also independently, or in addition to, the above optional substituents, Q₁ and Q₂ 25 may optionally and independently bear on any available carbon atom up to two further substituents independently selected from phenyl-C₁₋₄alkyl, phenyl-C₁₋₄alkoxy, phenyl, naphthyl, benzoyl and a 5-or 6-membered aromatic heterocycle (linked via a ring carbon atom and containing one to three heteroatoms independently selected from oxygen, sulphur and nitrogen); wherein said naphthyl, phenyl, benzoyl, 5-or 6-membered aromatic heterocyclic 30 substituents and the phenyl group in said phenyl-C₁₋₄alkyl and phenyl-C₁₋₄alkoxy substituents may optionally bear one or two substituents independently selected from halo, C₁₋₄alkyl and C₁₋₄alkoxy;

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or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

A suitable value for Q₁ or Q₂ when it is a 5-or 6-membered monocyclic moiety containing one to three heteroatoms independently selected from nitrogen, oxygen and sulphur, or a 9-or 10-membered bicyclic heterocyclic moiety containing one or two nitrogen
 5 heteroatoms and optionally containing a further one or two heteroatoms selected from nitrogen, oxygen and sulphur; is an aromatic heterocycle, for example, pyrrole, furan, thiophene, imidazole, oxazole, isoxazole, thiazole, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, p-isoxazine, quinolyl, isoquinolyl, cinnolyl, quinazolyl, quinoxalyl, phthalazinyl or naphthyridinyl, indole, isoindazole, benzoxazole, benzimidazole,
 10 benzothiazole, imidazo[1,5-a]pyridine, imidazo[1,2-c]pyrimidine, imidazo[1,2-a]pyrimidine, imidazo[1,5-a]pyrimidine; or a partially or fully hydrogenated derivative thereof such as for example, 1,2-dihydropyridyl, 1,2-dihydroquinolyl (all linked by a ring carbon atom), provided that for Q₁ an unstable aminal-type link with the amino link to the pyrimidine ring in (I) is not present.

15 When Q₁ is a 5-or 6-membered monocyclic moiety containing one to three heteroatoms independently selected from nitrogen, oxygen and sulphur, it will be appreciated that Q₁ is linked to the pyrimidine ring in (I) in such a way that Q₁ bears a substituent of the formula (Ia) or (Ia') which is not adjacent to the -NH-link. Thus, for example, 1,2,3-triazol-4-yl or 1,2,3-triazol-5-yl, are not suitable values for Q₁.

20 When Q₁ or Q₂ is a 9-or 10-membered bicyclic heterocyclic moiety containing one or two nitrogen atoms it will be appreciated that Q₁ or Q₂ may be attached from either of the two rings of the bicyclic heterocyclic moiety.

Conveniently when Q₁ or Q₂ is a heterocyclic moiety it is, for example, 2-pyridyl, 3-pyridyl, 4-pyridyl, 3-pyridazinyl, 4-pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl,
 25 5-pyrimidinyl, 2-pyrazinyl, 2-quinolyl, 3-quinolyl, 5-quinolyl, 6-quinolyl, 7-quinolyl, 1-isoquinolyl, 3-isoquinolyl, 6-isoquinolyl, 7-isoquinolyl, 3-cinnolyl, 6-cinnolyl, 7-cinnolyl, 2-quinazolyl, 4-quinazolyl, 6-quinazolyl, 7-quinazolyl, 2-quinoxalyl, 5-quinoxalyl, 6-quinoxalyl, 1-phthalazinyl, 6-phthalazinyl, 1,5-naphthyridin-2-yl, 1,5-naphthyridin-3-yl, 1,6-naphthyridin-3-yl, 1,6-naphthyridin-7-yl, 1,7-naphthyridin-3-yl,
 30 1,7-naphthyridin-6-yl, 1,8-naphthyridin-3-yl, 2,6-naphthyridin-6-yl or 2,7-naphthyridin-3-yl.

A suitable value for a ring substituent when it is a 5-or 6-membered aromatic heterocycle (linked via a ring carbon atom and containing one to three heteroatoms

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independently selected from oxygen, sulphur and nitrogen) is, for example, pyrrole, furan, thiophene, imidazole, oxazole, isoxazole, thiazole, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl or p-isoxazine.

A suitable value for Z in group (Ia) when it is a "nitrogen linked heteroaryl" is a mono
5 or bicyclic ring that has a degree of unsaturation, containing 4-12 atoms, at least one of which is selected from nitrogen, and optionally 1-3 further atoms are selected from nitrogen, sulphur or oxygen, wherein a -CH₂- group can optionally be replaced by a -C(O)-, and a ring sulphur and/or nitrogen atom may be optionally oxidised to form S-oxide(s) and/or an N-oxide. Suitably "nitrogen linked heteroaryl" is a monocyclic ring containing 5 or 6 atoms or a
10 bicyclic ring containing 9 or 10 atoms. The nitrogen link results in a neutral compound being formed. Suitable values for "nitrogen linked heteroaryl" include imidazol-1-yl, pyrrolin-1-yl, imidazolin-1-yl, pyrazolin-1-yl, triazol-1-yl, indol-1-yl, isoindol-2-yl, indolin-1-yl, benzimidazol-1-yl, pyrrol-1-yl or pyrazol-1-yl. Preferably "nitrogen linked heteroaryl" is imidazol-1-yl.

15 A suitable value for Z in group (Ia) when it is a "nitrogen linked heterocycle" is an unsaturated mono or bicyclic ring that contains 4-12 atoms, at least one of which is selected from nitrogen, and optionally 1-3 further atoms are selected from nitrogen, sulphur or oxygen, wherein a -CH₂- group can optionally be replaced by a -C(O)-, and a ring sulphur may be optionally oxidised to form S-oxide(s). Suitably "nitrogen linked heterocycle" is a monocyclic
20 ring containing 5 or 6 atoms or a bicyclic ring containing 9 or 10 atoms. Suitable values for "nitrogen linked heterocycle" include pyrrolidin-1-yl, piperidino, piperazin-1-yl, morpholino, thiomorpholino, homopiperidin-yl or homopiperazin-1-yl. Preferably a "nitrogen linked heterocycle" is pyrrolidin-1-yl, piperazin-1-yl or morpholino.

In this specification the term "alkyl" includes both straight and branched chain alkyl
25 groups but references to individual alkyl groups such as "propyl" are specific for the straight chain version only. An analogous convention applies to other generic terms.

Suitable values for the generic radicals (such as in substituents on Q₁ and Q₂) referred to above include those set out below :-

when it is **halo** is, for example, fluoro, chloro, bromo and iodo; **C₂₋₄alkenyl** is, for example,
30 vinyl and allyl; when it is **C₃₋₅alkenyl** is, for example, allyl and buten-3-yl; when it is **C₃₋₅alkynyl** is, for example, propyn-2-yl; when it is **C₂₋₄alkynyl** is, for example, ethynyl and propyn-2-yl; when it is **C₁₋₅alkanoyl** is, for example, formyl and acetyl; when it is

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C₁₋₄alkoxycarbonyl is, for example, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and tert-butoxycarbonyl; ; when it is **C₁₋₃alkyl** is, for example, methyl, ethyl, propyl, isopropyl; when it is **C₁₋₄alkyl** is, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or tert-butyl; when it is **C₁₋₆alkyl** is, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, 3-methylbutyl or hexyl; when it is **hydroxy-C₁₋₃alkyl** is, for example, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl and 3-hydroxypropyl; when it is **fluoro-C₁₋₃alkyl** is, for example, fluoromethyl, difluoromethyl, trifluoromethyl and 2-fluoroethyl; when it is **amino-C₁₋₃alkyl** is, for example, aminomethyl, 1-aminoethyl and 2-aminoethyl; when it is **C₁₋₄alkylamino-C₁₋₃alkyl** is, for example, methylaminomethyl, ethylaminomethyl, 1-methylaminoethyl, 2-methylaminoethyl, 2-ethylaminoethyl and 3-methylaminopropyl; when it is **N,N-di-(C₁₋₄alkyl)amino-C₁₋₃alkyl** is, for example, dimethylaminomethyl, diethylaminomethyl, 1-dimethylaminoethyl, 2-dimethylaminoethyl and 3-dimethylaminopropyl; when it is **cyano-C₁₋₄alkyl** is, for example, cyanomethyl, 2-cyanoethyl and 3-cyanopropyl; when it is **C₂₋₄alkanoyloxy-C₁₋₄alkyl** is, for example, acetoxymethyl, propionyloxymethyl, butyryloxymethyl, 2-acetoxyethyl and 3-acetoxypentyl; when it is **C₁₋₄alkoxy-C₁₋₃alkyl** is, for example, methoxymethyl, ethoxymethyl, 1-methoxyethyl, 2-methoxyethyl, 2-ethoxyethyl and 3-methoxypropyl; when it is **carboxy-C₁₋₄alkyl** is, for example, carboxymethyl, 1-carboxyethyl, 2-carboxyethyl and 3-carboxypropyl; when it is **C₁₋₄alkoxycarbonyl-C₁₋₄alkyl** is, for example, methoxycarbonylmethyl, ethoxycarbonylmethyl, tert-butoxycarbonylmethyl, 1-methoxycarbonylethyl, 1-ethoxycarbonylethyl, 2-methoxycarbonylethyl, 2-ethoxycarbonylethyl, 3-methoxycarbonylpropyl and 3-ethoxycarbonylpropyl; when it is **carbamoyl-C₁₋₄alkyl** is, for example, carbamoylmethyl, 1-carbamoylethyl, 2-carbamoylethyl and 3-carbamoylpropyl; when it is **N-C₁₋₄alkylcarbamoyl-C₁₋₄alkyl** is, for example, *N*-methylcarbamoylmethyl, *N*-ethylcarbamoylmethyl, *N*-propylcarbamoylmethyl, 1-(*N*-methylcarbamoyl)ethyl, 1-(*N*-ethylcarbamoyl)ethyl, 2-(*N*-methylcarbamoyl)ethyl, 2-(*N*-ethylcarbamoyl)ethyl and 3-(*N*-methylcarbamoyl)propyl; when it is **N,N-di-(C₁₋₄alkyl)-carbamoyl-C₁₋₄alkyl** is, for example, *N,N*-dimethylcarbamoylmethyl, *N*-ethyl-*N*-methylcarbamoylmethyl, *N,N*-diethylcarbamoylmethyl, 1-(*N,N*-dimethylcarbamoyl)ethyl, 1-(*N,N*-diethylcarbamoyl)ethyl, 2-(*N,N*-dimethylcarbamoyl)ethyl, 2-(*N,N*-diethylcarbamoyl)ethyl and 3-(*N,N*-dimethylcarbamoyl)propyl; when it is **pyrrolidin-1-yl-C₁₋₃alkyl** is, for example,

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- pyrrolidin-1-ylmethyl and 2-pyrrolidin-1-ylethyl; when it is **piperidin-1-yl-C_{1,3}alkyl** is, for example, piperidin-1-ylmethyl and 2-piperidin-1-ylethyl; when it is **piperazin-1-yl-C_{1,3}alkyl** is, for example, piperazin-1-ylmethyl and 2-piperazin-1-ylethyl; when it is **morpholino-C_{1,3}alkyl** is, for example, morpholinomethyl and 2-morpholinoethyl; when it is
- 5 **thiomorpholino-C_{1,3}alkyl** is, for example, thiomorpholinomethyl and 2-thiomorpholinoethyl; when it is **C_{1,4}alkoxy** is, for example, methoxy, ethoxy, propoxy, isopropoxy or butoxy; when it is **cyano-C_{1,4}alkoxy** is, for example, cyanomethoxy, 1-cyanoethoxy, 2-cyanoethoxy and 3-cyanopropoxy; when it is **carbamoyl-C_{1,4}alkoxy** is, for example, carbamoylmethoxy, 1-carbamoylethoxy, 2-carbamoylethoxy and 3-carbamoylpropoxy; when it is
- 10 **N-C_{1,4}alkylcarbamoyl-C_{1,4}alkoxy** is, for example, *N*-methylcarbamoylmethoxy, *N*-ethylcarbamoylmethoxy, 2-(*N*-methylcarbamoyl)ethoxy, 2-(*N*-ethylcarbamoyl)ethoxy and 3-(*N*-methylcarbamoyl)propoxy; when it is ***N,N*-di-(C_{1,4}alkyl)-carbamoyl-C_{1,4}alkoxy** is, for example, *N,N*-dimethylcarbamoylmethoxy, *N*-ethyl-*N*-methylcarbamoylmethoxy, *N,N*-diethylcarbamoylmethoxy, 2-(*N,N*-dimethylcarbamoyl)ethoxy,
- 15 2-(*N,N*-diethylcarbamoyl)ethoxy and 3-(*N,N*-dimethylcarbamoyl)propoxy; when it is **2-C_{1,4}alkylaminoethoxy** is, for example, 2-(methylamino)ethoxy, 2-(ethylamino)ethoxy and 2-(propylamino)ethoxy; when it is **2-*N,N*-di-(C_{1,4}alkyl)aminoethoxy** is, for example, 2-(dimethylamino)ethoxy, 2-(*N*-ethyl-*N*-methylamino)ethoxy, 2-(diethylamino)ethoxy and 2-(dipropylamino)ethoxy; when it is **C_{1,4}alkoxycarbonyl-C_{1,4}alkoxy** is, for example,
- 20 methoxycarbonylmethoxy, ethoxycarbonylmethoxy, 1-methoxycarbonylethoxy, 2-methoxycarbonylethoxy, 2-ethoxycarbonylethoxy and 3-methoxycarbonylpropoxy; when it is **halo-C_{1,4}alkoxy** is, for example, difluoromethoxy, trifluoromethoxy, 2-fluoroethoxy, 2-chloroethoxy, 2-bromoethoxy, 3-fluoropropoxy and 3-chloropropoxy; when it is **C_{1,4}alkanoyloxy-C_{1,4}alkoxy** is, for example, 2-acetoxyethoxy, 2-propionyloxyethoxy,
- 25 2-butyryloxyethoxy and 3-acetoxypropoxy; when it is **2-C_{1,4}alkoxyethoxy** is, for example, 2-methoxyethoxy, 2-ethoxyethoxy; when it is **carboxy-C_{1,4}alkoxy** is, for example, carboxymethoxy, 1-carboxyethoxy, 2-carboxyethoxy and 3-carboxypropoxy; when it is **C_{3,5}alkenyloxy** is, for example, allyloxy; when it is **C_{3,5}alkynyloxy** is, for example, propynyloxy; when it is **C_{1,4}alkylthio** is, for example, methylthio, ethylthio or propylthio;
- 30 when it is **C_{1,4}alkylsulphinyl** is, for example, methylsulphinyl, ethylsulphinyl or propylsulphinyl; when it is **C_{1,4}alkylsulphonyl** is, for example, methylsulphonyl, ethylsulphonyl or propylsulphonyl; when it is ***N*-C_{1,4}alkylcarbamoyl** is, for example

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N-methylcarbamoyl, *N*-ethylcarbamoyl and *N*-propylcarbamoyl; when it is *N,N*-di-(C₁₋₄alkyl)-carbamoyl is, for example *N,N*-dimethylcarbamoyl, *N*-ethyl-*N*-methylcarbamoyl and *N,N*-diethylcarbamoyl; when it is C₁₋₄alkylamino is, for example, methylamino, ethylamino or propylamino; when it is *N,N*-di-(C₁₋₄alkyl)amino is, for example, dimethylamino, *N*-ethyl-*N*-methylamino, diethylamino, *N*-methyl-*N*-propylamino or dipropylamino; when it is C₂₋₄alkanoylamino is, for example, acetamido, propionamido or butyramido; when it is phenyl-C₁₋₄alkyl is, for example benzyl or 2-phenylethyl; when it is phenyl-C₁₋₄alkoxy is, for example benzyloxy.

A suitable pharmaceutically acceptable salt of a pyrimidine derivative of the invention is, for example, an acid-addition salt of a pyrimidine derivative of the invention which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric or maleic acid. In addition a suitable pharmaceutically acceptable salt of a pyrimidine derivative of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

The compounds of the formula (I) may be administered in the form of a pro-drug which is broken down in the human or animal body to give a compound of the formula (I). Examples of pro-drugs include *in vivo* hydrolysable esters of a compound of the formula (I).

An *in vivo* hydrolysable ester of a compound of the formula (I) containing carboxy or hydroxy group is, for example, a pharmaceutically acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically acceptable esters for carboxy include C₁₋₆alkoxymethyl esters for example methoxymethyl, C₁₋₆alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C₁₋₆cycloalkoxycarbonyloxyC₁₋₆alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C₁₋₆alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

An *in vivo* hydrolysable ester of a compound of the formula (I) containing a hydroxy group includes inorganic esters such as phosphate esters (including phosphoramidic cyclic

- 9 -

esters) and α -acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester breakdown to give the parent hydroxy group/s. Examples of α -acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxy-methoxy. A selection of *in vivo* hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, 5 phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and *N*-(dialkylaminoethyl)-*N*-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl. Examples of substituents on benzoyl include morpholino and piperazino linked from a ring nitrogen atom via a methylene group to the 3-or 4-position of the benzoyl ring.

10 Some compounds of the formula (I) may have chiral centres and/or geometric isomeric centres (E-and Z-isomers), and it is to be understood that the invention encompasses all such optical, diastereo-isomers and geometric isomers (and mixtures thereof) that possess CDK inhibitory activity.

The invention relates to any and all tautomeric forms of the compounds of the formula 15 (I) that possess CDK inhibitory activity.

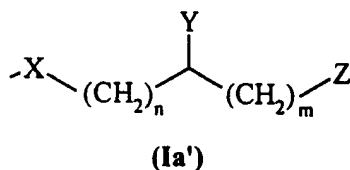
It is also to be understood that certain compounds of the formula (I) can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which possess CDK inhibitory activity.

20 According to a further feature of the invention there is provided a pyrimidine derivative of the formula (I) (as depicted above) wherein:

V is O or S;

Q₁ and Q₂ are independently selected from phenyl, naphthyl, a 5-or 6-membered monocyclic moiety (linked via a ring carbon atom and containing one to three heteroatoms 25 independently selected from nitrogen, oxygen and sulphur); and a 9-or 10-membered bicyclic heterocyclic moiety (linked via a ring carbon atom and containing one or two nitrogen heteroatoms and optionally containing a further one or two heteroatoms selected from nitrogen, oxygen and sulphur); provided that there is an available carbon atom in Q₁ such that the substituent of formula (Ia') (defined hereinbelow) is not adjacent to the -NH-link; 30 and Q₁ is substituted on an available carbon atom not adjacent to the -NH-link one substituent of the formula (Ia'), and Q₂ may optionally bear on any available carbon atom further substituents of the formula (Ia'):

- 10 -



wherein

X is CH₂, O, NH or S;

5 Y is H or as defined for Z;

Z is OH, SH, NH₂, C₁₋₄alkoxy, C₁₋₄alkylthio, -NHC₁₋₄alkyl, -N(C₁₋₄alkyl)₂,
pyrrolidin-1-yl, piperidin-1-yl, piperazin-1-yl, morpholino or thiomorpholino;

n is 1, 2 or 3;

m is 1, 2 or 3;

10 and Q₁ and Q₂ may optionally and independently bear on any available carbon atom up to four substituents independently selected from halo, hydroxy, thio, nitro, carboxy, cyano, C₂₋₄alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent], C₂₋₄alkynyl, C₁₋₃alkanoyl, C₁₋₄alkoxycarbonyl, C₁₋₆alkyl, hydroxy-C₁₋₃alkyl, fluoro-C₁₋₄alkyl, amino-C₁₋₃alkyl, C₁₋₄alkylamino-C₁₋₃alkyl, *N,N*-di-(C₁₋₄alkyl)amino-C₁₋₃alkyl,
15 cyano-C₁₋₄alkyl, C₂₋₄alkanoyloxy-C₁₋₄alkyl, C₁₋₄alkoxy-C₁₋₃alkyl, carboxy-C₁₋₄alkyl, C₁₋₄alkoxycarbonyl-C₁₋₄alkyl, carbamoyl-C₁₋₄alkyl, *N*-C₁₋₄alkylcarbamoyl-C₁₋₄alkyl, *N,N*-di-(C₁₋₄alkyl)-carbamoyl-C₁₋₄alkyl, pyrrolidin-1-yl-C₁₋₃alkyl, piperidin-1-yl-C₁₋₃alkyl, piperazin-1-yl-C₁₋₃alkyl, morpholino-C₁₋₃alkyl, thiomorpholino-C₁₋₃alkyl, piperazin-1-yl, morpholino, thiomorpholino, C₁₋₄alkoxy, cyano-C₁₋₄alkoxy, carbamoyl-C₁₋₄alkoxy,
20 *N*-C₁₋₄alkylcarbamoyl-C₁₋₄alkoxy, *N,N*-di-(C₁₋₄alkyl)-carbamoyl-C₁₋₄alkoxy, 2-aminoethoxy, 2-C₁₋₄alkylaminoethoxy, 2-*N,N*-di-(C₁₋₄alkyl)aminoethoxy, C₁₋₄alkoxycarbonyl-C₁₋₄alkoxy, halo-C₁₋₄alkoxy, 2-hydroxyethoxy, C₂₋₄alkanoyloxy-C₂₋₄alkoxy, 2-C₁₋₄alkoxyethoxy, carboxy-C₁₋₄alkoxy, C₃₋₅alkenyloxy, C₃₋₅alkynyloxy, C₁₋₄alkylthio, C₁₋₄alkylsulphinyl, C₁₋₄alkylsulphonyl, ureido (H₂N-CO-NH-), C₁₋₄alkylNH-CO-NH-,
25 *N,N*-di-(C₁₋₄alkyl)N-CO-NH-, C₁₋₄alkylNH-CO-N(C₁₋₄alkyl)-, *N,N*-di-(C₁₋₄alkyl)N-CO-N(C₁₋₄alkyl)-, carbamoyl, *N*-(C₁₋₄alkyl)carbamoyl, *N,N*-di-(C₁₋₄alkyl)carbamoyl, amino, C₁₋₄alkylamino, *N,N*-di-(C₁₋₄alkyl)amino, C₂₋₄alkanoylamino,

and also independently, or in addition to, the above optional substituents, Q₁ and Q₂

30 may optionally and independently bear on any available carbon atom up to two further

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substituents independently selected from phenyl-C₁₋₄alkyl, phenyl-C₁₋₄alkoxy, phenyl, naphthyl, benzoyl and a 5-or 6-membered aromatic heterocycle (linked via a ring carbon atom and containing one to three heteroatoms independently selected from oxygen, sulphur and nitrogen); wherein said naphthyl, phenyl, benzoyl, 5-or 6-membered aromatic heterocyclic substituents and the phenyl group in said phenyl-C₁₋₄alkyl and phenyl-C₁₋₄alkoxy substituents may optionally bear one or two substituents independently selected from halo, C₁₋₄alkyl and C₁₋₄alkoxy;
 or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

In another embodiment there is provided a pyrimidine derivative of the formula (I), or
 10 pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as described above, but where when X is CH₂ and Y is H either
 a) Z is not C₁₋₄alkoxy when Q₁ is phenyl or
 b) Z is not OH when Q₁ is a bicyclic heterocyclic moiety.

Particular preferred compounds of the invention comprise a pyrimidine derivative of
 15 the formula (I), or pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, wherein Q₁, Q₂, V, X, Y, Z, m and n have any of the meanings defined hereinbefore, or any of the following values :-

- (a) Q₁ is preferably phenyl;
- (b) Q₂ is preferably phenyl;
- 20 (c) V is preferably O;
- (d) Preferably in the substituent of formula (Ia') X is O, Y is OH and Z is -N(C₁₋₄alkyl)₂, pyrrolidin-1-yl or piperidin-1-yl; preferably n is 1 and m is 1;
- (e) Preferably in the substituent of formula (Ia) X is O, Y¹ is OH, Y² is H and Z is -N(C₁₋₄alkyl)₂, pyrrolidin-1-yl or piperidin-1-yl; preferably n is 1 and m is 1;
- 25 (f) Most preferably the substituent of formula (Ia') is 3-dimethylamino-2-hydroxypropoxy;
- (g) Most preferably the substituent of formula (Ia) is 3-dimethylamino-2-hydroxypropoxy;
- (h) Preferably there is one substituent of formula (Ia'), i.e. preferably Q₂ does not bear a
 30 substituent of formula (Ia');
- (i) Preferably there is one substituent of formula (Ia), i.e. preferably Q₂ does not bear a substituent of formula (Ia);

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- (j) When Q_1 is phenyl the substituent of formula (Ia') must be in either the para- or meta-position relative to the -NH-, preferably in the para-position;
- (k) When Q_1 is phenyl the substituent of formula (Ia) must be in either the para- or meta-position relative to the -NH-, preferably in the para-position;
- 5 (l) Preferable further substituents for Q_2 include halo (especially chloro), C_{1-4} alkoxy (especially methoxy), C_{1-4} alkyl (especially methyl) or trifluoromethyl;
- (m) Preferably the ring Q_2 when not bearing the substituent of formula (Ia') is optionally substituted by one or two further substituents, preferably halo (especially chloro), C_{1-4} alkoxy (especially methoxy), C_{1-4} alkyl (especially methyl) or trifluoromethyl.
- 10 (n) Preferably the ring Q_2 when not bearing the substituent of formula (Ia) is optionally substituted by one or two further substituents, preferably halo (especially chloro), C_{1-4} alkoxy (especially methoxy), C_{1-4} alkyl (especially methyl) or trifluoromethyl.
- (o) More preferably Q_2 is optionally substituted by one or two groups selected from chloro, bromo, methoxy, methyl or trifluoromethyl.
- 15 A preferred compound of the invention is a pyrimidine derivative of the formula (I), or pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, wherein:
- Q_1 is phenyl and Q_2 is phenyl; V is O;
- Q_1 bears one substituent of formula (Ia') (especially 3-dimethylamino-2-hydroxypropoxy), preferably in the para-position;
- 20 Q_2 optionally bears one or two substituents independently selected from halo (especially chloro), C_{1-4} alkoxy (especially methoxy), C_{1-4} alkyl (especially methyl) and trifluoromethyl.
- Another preferred compound of the invention is a pyrimidine derivative of the formula (I), or pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, wherein:
- Q_1 is phenyl and Q_2 is phenyl; V is O;
- 25 Q_1 bears one substituent of formula (Ia) (especially 3-dimethylamino-2-hydroxypropoxy), preferably in the para-position;
- Q_2 optionally bears one or two substituents independently selected from halo (especially chloro), C_{1-4} alkoxy (especially methoxy), C_{1-4} alkyl (especially methyl) and trifluoromethyl.
- A specific preferred compound of the invention is the pyrimidine derivative of the
- 30 formula (I), being Example 6 (described hereinafter); or pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.
- In a further aspect of the invention preferred compounds of the invention include any

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one of the Examples or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

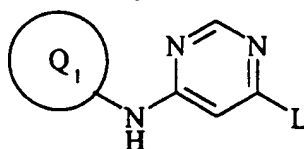
Preferred aspects of the invention are those which relate to the compound or a pharmaceutically acceptable salt thereof.

- 5 A pyrimidine derivative of the formula (I), or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof, may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Such processes, when used to prepare a pyrimidine derivative of the formula (I), or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof, are provided as a further feature of the invention and are illustrated
- 10 by the following representative examples in which (unless otherwise stated) Q_1 , Q_2 , V, X, Y, Z, m and n have any of the meanings defined hereinbefore for a pyrimidine derivative of the formula (I), and unless another substituent is drawn on ring Q_1 or Q_2 the ring may bear any of the substituents described hereinbefore (optionally protected as necessary). Where a substituent is drawn on ring Q_1 , this includes (unless stated otherwise) the possibilities (as
- 15 appropriate) of the substituent being on ring Q_2 in addition to, or instead of, the substituent being on ring Q_1 . Necessary starting materials may be obtained by standard procedures of organic chemistry (see, for example, Advanced Organic Chemistry (Wiley-Interscience), Jerry March - also useful for general guidance on reaction conditions and reagents). The preparation of such starting materials is described within the accompanying non-limiting processes and
- 20 Examples. Alternatively, necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist.

Thus, as a further feature of the invention there are provided the following processes for preparing compounds of formula (I) which comprises of :-

Process a)

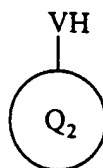
- 25 reacting a pyrimidine of formula (II):



(II)

wherein L is a displaceable group as defined below, with a compound of formula (III):

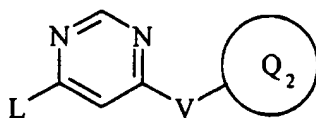
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(III)

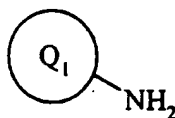
Process b)

reaction of a pyrimidine of formula (IV):



(IV)

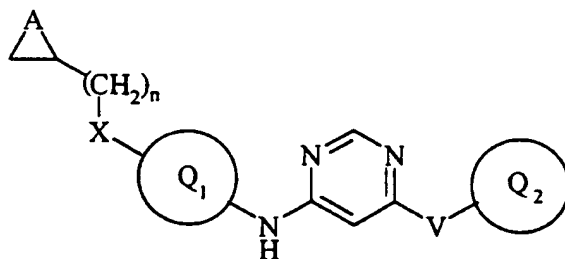
wherein L is a displaceable group as defined below, with a compound of formula (V):



(V)

10 Process c)

for compounds of formula (I) where $m = 1$ and Y is OH, NH₂ or SH, reaction of a 3-membered heteroalkyl ring of formula (VI):



(VI)

15 wherein A is O, S or NH;

with a nucleophile of formula (VII):

Z-D

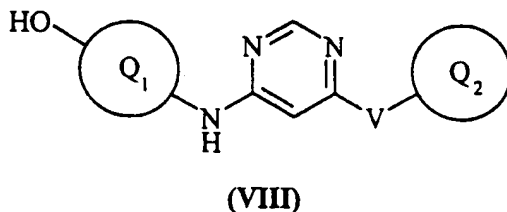
(VII)

wherein D is H or a suitable counter-ion;

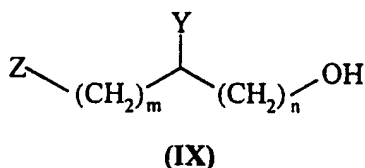
- 15 -

Process d)

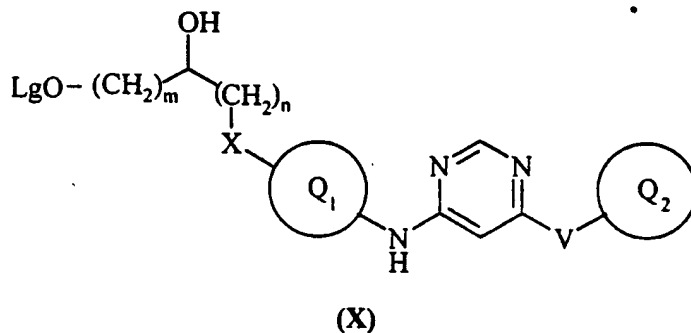
for compounds of formula (I) where X is oxygen, by reaction of an alcohol of formula (VIII):



5 with an alcohol of formula (IX):

Process e)

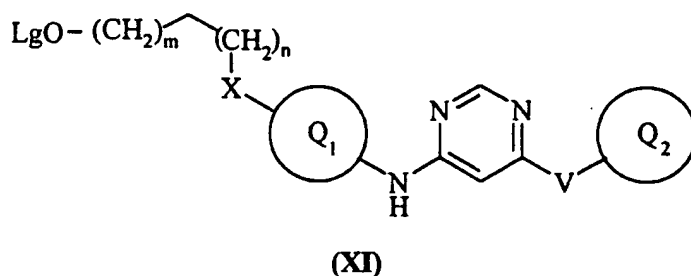
for compounds of formula (I) wherein X is -CH₂-, -O-, -NH- or -S-, Y¹ is OH, Y² is H and m
10 is 2 or 3; reaction of a compound of formula (X):



wherein LgO is a leaving group as defined below; with a nucleophile of formula (VII);

Process f)

15 for compounds of formula (I) wherein X is -CH₂-, -O-, -NH- or -S-, Y¹ and Y² are H; n is 1, 2 or 3 and m is 1, 2 or 3; reaction of a compound of formula (XI):

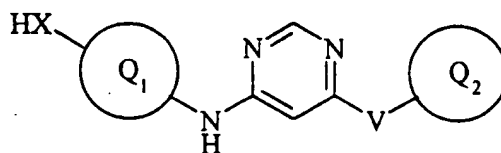


wherein LgO is a leaving group as defined below; with a nucleophile of formula (VII);

- 16 -

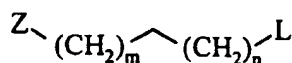
Process g)

for compounds of formula (I) wherein X is -O-, -NH- or -S-; Y¹ and Y² are H; n is 1, 2 or 3 and m is 1, 2 or 3; reaction of a compound of formula (XII):



(XII)

with a compound of formula (XIII)



(XIII)

wherein L is a displaceable group as defined below;

10 Process h)

for compounds of formula (I) in which Z is HS-, by conversion of a thioacetate group in a corresponding compound;

and thereafter if necessary:

i) converting a compound of the formula (I) into another compound of the formula (I);

15 ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester.

L is a displaceable group. suitable values for L are for example, a halo or sulphonyloxy group. for example a chloro, bromo, methanesulphonyloxy or toluene-4-sulphonyloxy group. Alternative suitable groups for L include halo, mesyl,

20 methylthio and methylsulphinyl.

D is hydrogen or a counter-ion. When D is a counter-ion, suitable values for D include sodium and potassium.

LgO is a leaving group. Suitable values for LgO include mesylate and tosylate.

Specific reaction conditions for the above reactions are as follows:-

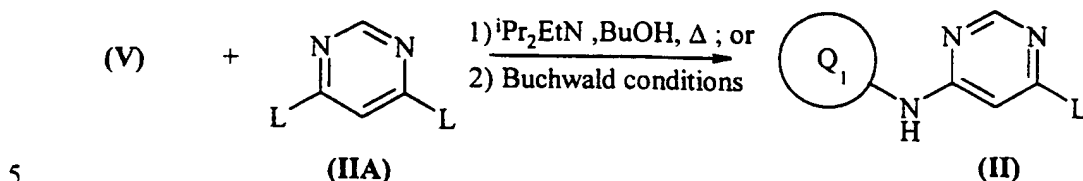
25 Process a)

Pyrimidines of formula (II) and compounds of formula (III) may be reacted together, optionally in the presence of a suitable base, for example an inorganic base such as potassium carbonate. The reaction is preferably carried out in a suitable inert solvent or diluent, for example dichloromethane (DCM), acetonitrile, butanol, tetramethylene sulphone.

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tetrahydrofuran, 1,2-dimethoxyethane, *N,N*-dimethylformamide, *N,N*-dimethylacetamide or *N*-methylpyrrolidin-2-one, and at a temperature in the range, for example, 0° to 150°C, conveniently at or near ambient temperature.

Pyrimidines of the formula (II) may be prepared according to the following scheme:



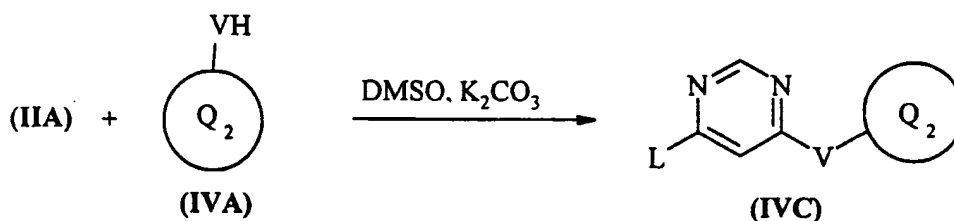
wherein L is a displaceable group as defined above.

Compounds of formula (V) and (III) are commercially available, are prepared by processes known in the art or are obtainable by analogous procedures to those illustrated within this specification which are within the ordinary skill of an organic chemist.

10 Process b)

Pyrimidines of formula (IV) and compounds of formula (V) may be reacted together in the presence of a suitable solvent for example a ketone such as acetone or an alcohol such as ethanol or butanol or an aromatic hydrocarbon such as toluene or *N*-methyl pyrrolidine, or a solvent such as tetramethylene sulphone, optionally in the presence of a suitable acid (such as those defined for process a) above or a Lewis acid) or base (such as Hunig's base or calcium carbonate) and at a temperature in the range of 0°C to reflux, preferably reflux.

Pyrimidines of formula (IV) are prepared according to the following scheme:



wherein L is a displaceable group as defined above.

The compounds of formula (IVA), (III) and (V) are commercially available or are prepared by processes known in the art.

Process c)

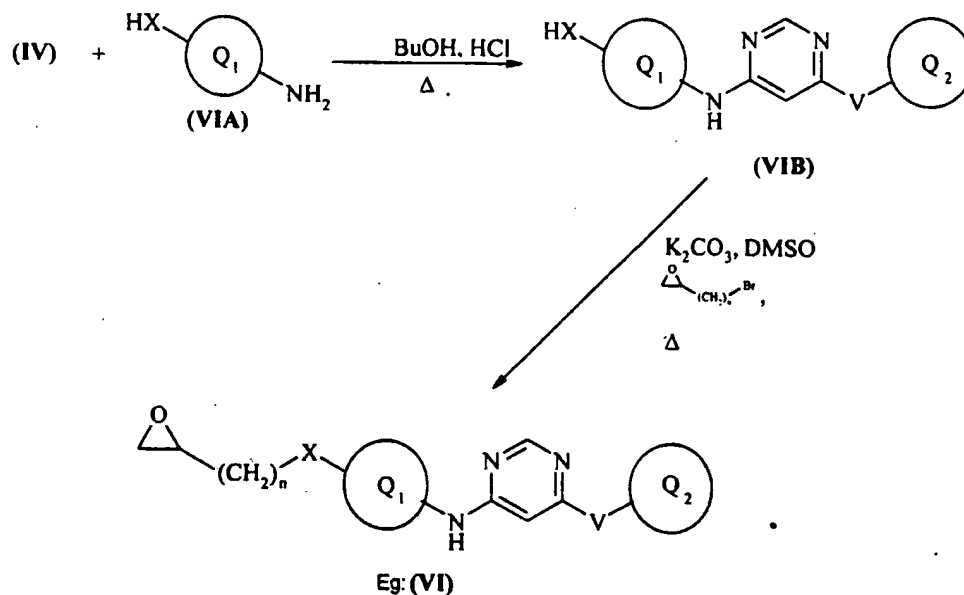
Three-membered heteroalkyl ring containing compounds of formula (VI) and nucleophiles of formula (VII) are reacted together at a temperature in the range of 20° to

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100°C, preferably 20° to 50°C, optionally in the presence of a suitable solvent, for example *N,N*-dimethylformamide, dimethyl sulfoxide or tetrahydrofuran.

Compounds of formula (VI) may be prepared according to the following schemes:

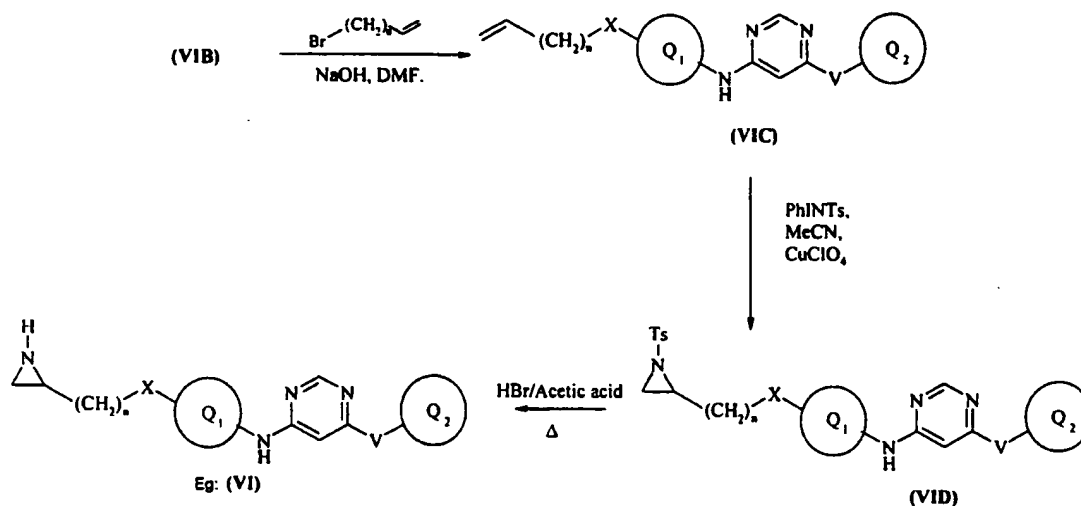
Scheme I) for compounds of formula (VI) where A is O₁ and X is not carbon:



5

The conversion of (VIB) to (VI) may also be achieved by reaction with $\text{Br} \text{---} (\text{CH}_2)_n \text{---} \text{CHO}$, or an equivalent ester, in DMF and the presence of a base, followed by reaction with a sulphur ylide such as $(\text{Me}_2\text{SOCH}_2)$ in an inert solvent such as THF (see scheme V).

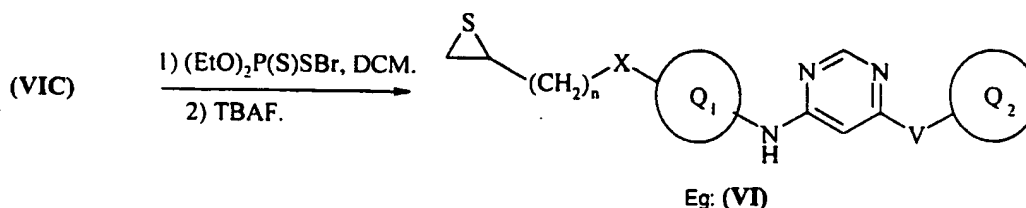
10 Scheme II) for compounds of formula (VI) where A is NH₁ and X is not carbon:



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(for PhINTs see, for example, Tet. Let., 1997, 38 (39), 6897-6900; compounds of formula (VIC) may also be oxidised to the epoxide using conditions similar to that in *Scheme IV* below);

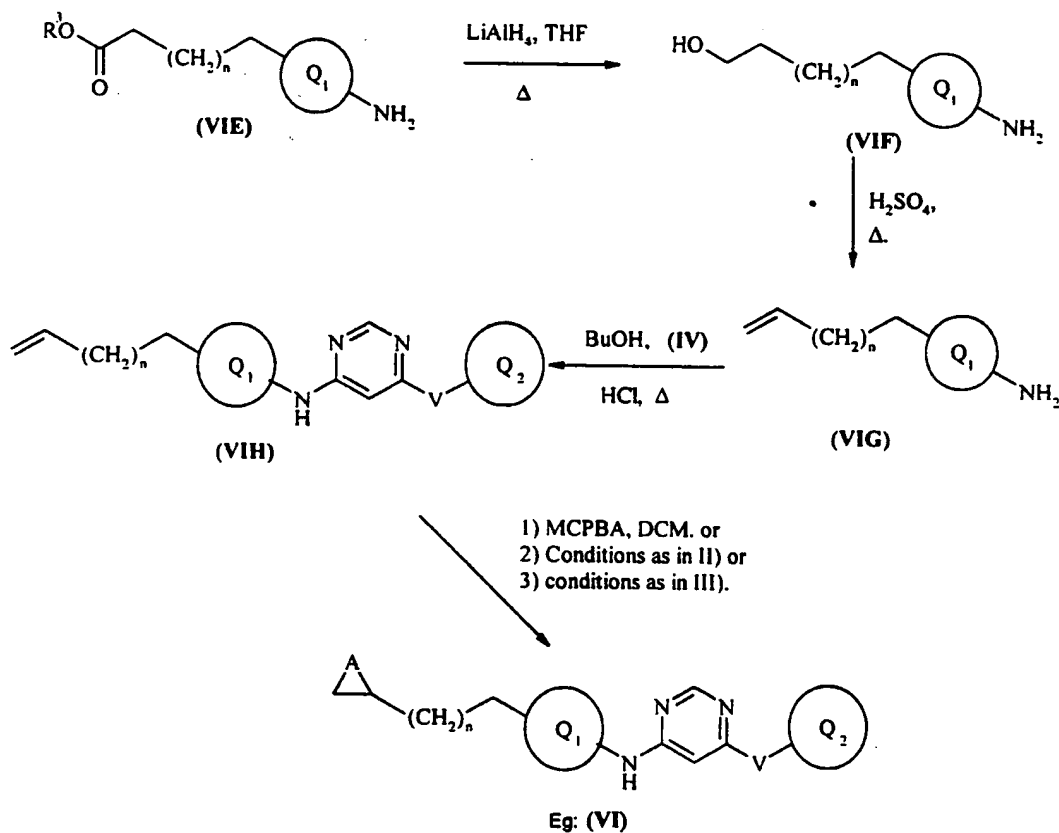
Scheme III for compounds of formula (VIII) where A is S, and X is not carbon:



5

(for example see *Synlett*, 1994, 267-268);

Scheme IV for compounds of formula (VI) where X is carbon

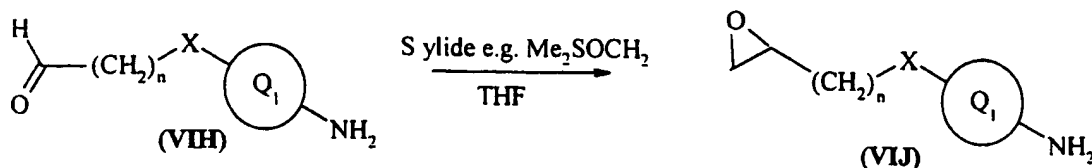


wherein R³ together with the -COO-group to which it is attached forms an ester

moiety, for example a methyl ester or an ethyl ester.

Scheme V for compounds of formula (VI) wherein X is CH₂, O, NH or S; Y is OH; n is 1, 2 or 3 and m is 1 :

- 20 -



(VIJ) is reacted with (IV) (see Scheme I) to give (VI).

An equivalent ester of (VIH) may also be used. See also Russ. Chem. Rev. 47, 975-990, 1978.

- 5 Compounds of formula (VIH), (VII) and (VIA) and (VIE) are commercially available or are prepared by processes known in the art.

Process d)

Alcohols of formula (VIII) and (IX) can be reacted together under standard Mitsunobu conditions. For example in the presence of diethyl azodicarboxylate and triphenyl
 10 phosphine, in a suitable solvent such as dichloromethane, toluene or tetrahydrofuran, and at a temperature in the range of 0° to 80°C, preferably in the range of 20° to 60°C. Alternatively, alcohols of formula (VIII) may be alkylated with a suitable compound of formula (IX) in which the terminal hydroxy group has been replaced by a suitable leaving group.

Alcohols of formula (VIII) are made according to the *Scheme I* above for the
 15 synthesis of intermediate (VIB) (where X is oxygen).

Alcohols of formula (IX) are commercially available or are made by processes known in the art.

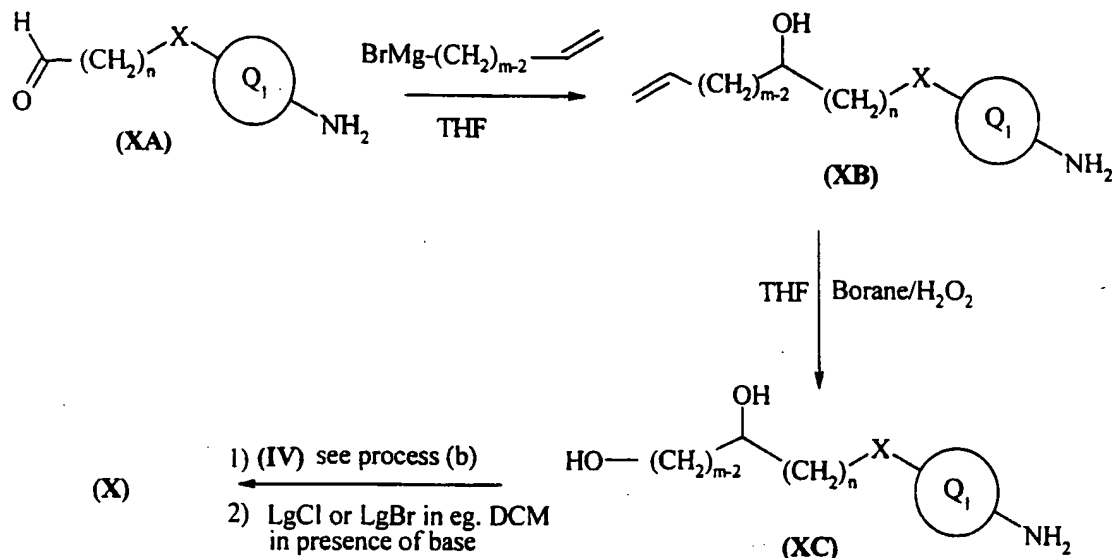
In a process analogous to process d), compounds in which X is -S- may be prepared by reaction of a compound of formula (VIII) in which the hydroxy group is -SH, with a
 20 compound of formula (IX) in which the hydroxy group is a leaving group such as mesylate or tosylate.

Process e)

Compounds of formula (X) wherein X is -CH₂-, -O-, -NH- or -S-; Y¹ is OH, Y² is H and m is 2 or 3 and nucleophiles of formula (VII) are reacted together at a temperature in the
 25 range of 20° to 100°C, preferably 20° to 50°C, optionally in the presence of a suitable solvent, for example *N,N*-dimethylformamide, dimethyl sulphoxide or tetrahydrofuran, and optionally in the presence of a suitable base, such as potassium carbonate.

Compounds of formula (X) are prepared according to the following scheme (m is 2 or 3):

- 21 -



The order of steps 1) and 2) in the final step may be reversed. A suitable base for step 2) is triethylamine.

Compounds of formula (XA) and (VII) are commercially available or are prepared by processes known in the art. For example, compounds of formula (XA) in which X is -NH-, -O- or -S- may be prepared by reaction of a compound of formula (VIA) with a suitable haloaldehyde or equivalent ester under standard conditions for such reactions.

Process f)

Compounds of formula (XI) and nucleophiles of formula (VII) are reacted together as described for process e) above.

Compounds of formula (XI) are prepared in an analogous manner to step 2) in the final step of the process for preparing compounds of formula (X) above. The necessary primary alcohol starting materials are commercially available or are prepared by processes known in the art.

15 Process g)

Compounds of formula (XII) and (XIII) are reacted in an inert solvent such as DMF in the presence of a base such as potassium carbonate.

Compounds of formula (XII) are of the same generic formula as compounds of formula (VIB) described herein and are prepared as described for those compounds (see Scheme I). Compounds of formula (XIII) are commercially available or are prepared by processes known in the art.

Process h)

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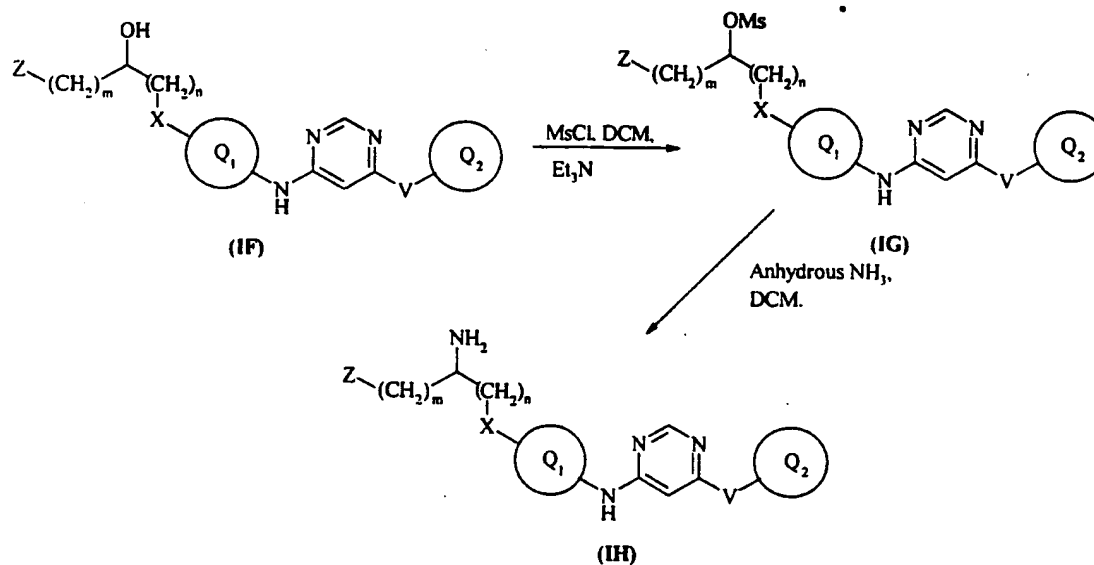
For the compounds of formula (I) in which Z is SH, the conversion of a thioacetate group in a corresponding compound is carried out as described herein for the conversion of compounds of formula (IJ) into (IK).

- Suitable starting materials containing a thioacetate group are prepared from
- 5 corresponding compounds containing a leaving group such as mesylate or tosylate (prepared using standard conditions from the corresponding hydroxy compound) using thiol acetic acid as described herein for the conversion of compounds of formula (IG) into (IJ).

Examples of conversions of a compound of formula (I) into another compound of formula (I) are:

- 10 Conversion of one side chain of formula (Ia) or (Ia') into another side chain of formula (Ia) or (Ia'), for example:

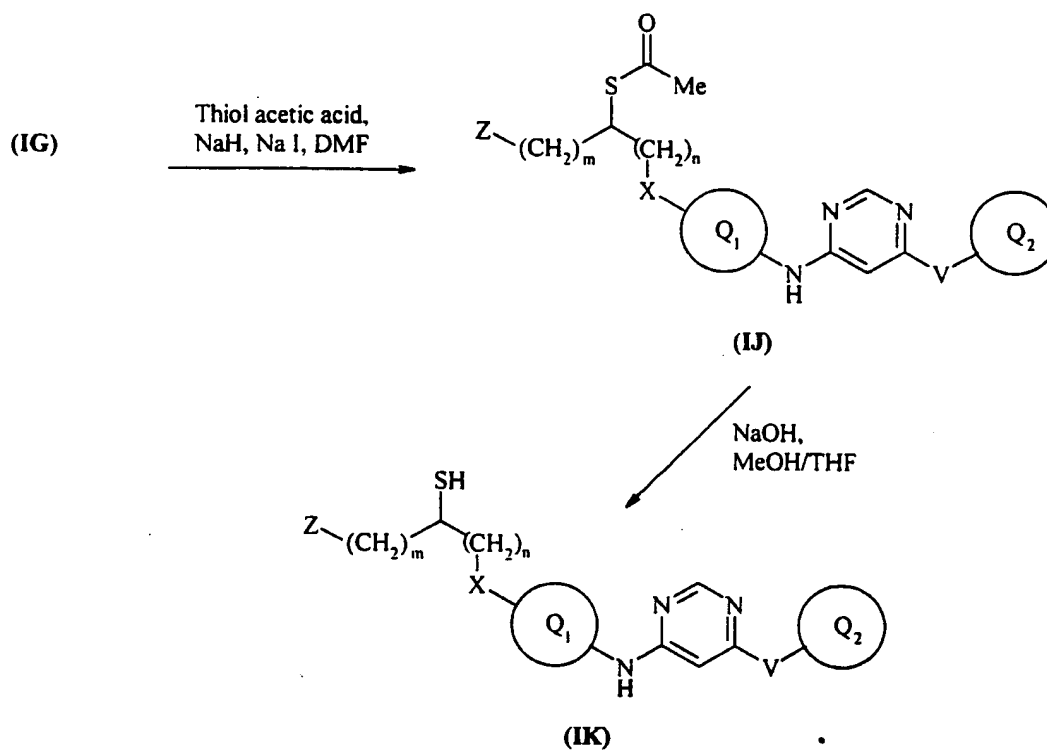
Conversion I) for compounds of formula (I) where Y² is H and Y¹ is NH₂ (depicted below using ammonia), C₁₋₄alkoxy, C₁₋₄alkylthio, -NHC₁₋₄alkyl, -N(C₁₋₄alkyl)₂, pyrrolidin-1-yl, piperidin-1-yl, piperazin-1-yl, morpholino or thiomorpholino;



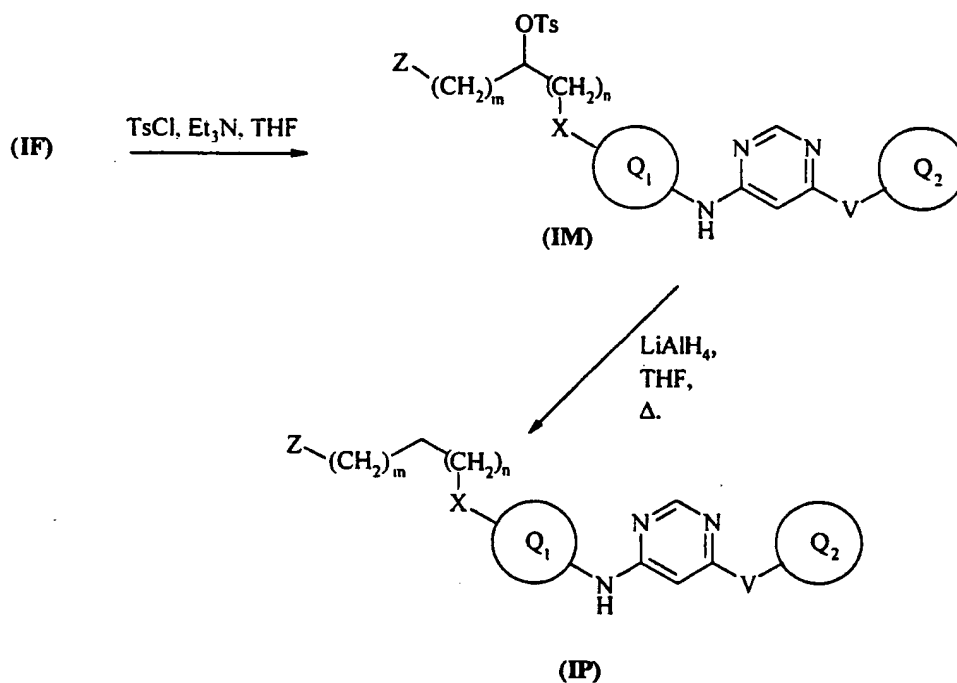
15

Conversion II) for compounds of formula (I) where Y¹ is S and Y² is H:

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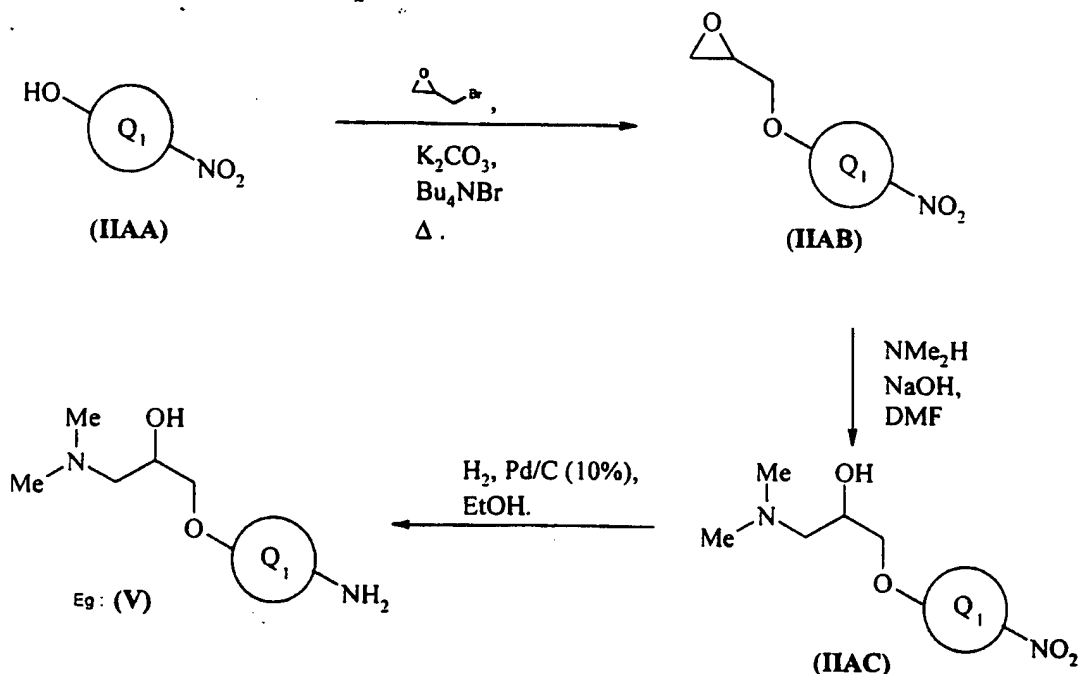


Conversion III for compounds of formula (I) where Y¹ is H and Y² is H:



The skilled reader will appreciate that the manipulation of the side chain (Ia) or (Ia') described, for example, in processes c) and d) above may also be performed on intermediates, for example to make intermediates of formula (II), (IIA), (IIB), or (V). For example:

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It will be appreciated that certain of the various ring substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halo group. Particular examples of modifications include the reduction of a nitro group to an amino group by for example, catalytic hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those

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skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Green, Protective Groups in Organic Synthesis, John Wiley and Sons, 1991). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

- 5 A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting
- 10 group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an
- 15 arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.
- 20 A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with
- 25 a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

- 30 A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic

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acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

5 Many of the intermediates defined herein are novel, for example, those of the formula II and IV and these are provided as a further feature of the invention.

As stated hereinbefore the pyrimidine derivative defined in the present invention possesses anti-cell-proliferation activity such as anti-cancer activity which is believed to arise from the CDK inhibitory activity of the compound. These properties may be assessed, for
10 example, using the procedure set out below:-

Assay

The following abbreviations have been used :-

HEPES is *N*-[2-Hydroxyethyl]piperazine-*N'*-[2-ethanesulfonic acid]

DTT is Dithiothreitol

15 PMSF is Phenylmethylsulfonyl fluoride

The compounds were tested in an *in vitro* kinase assay in 96 well format using Scintillation Proximity Assay (SPA -obtained from Amersham) for measuring incorporation of [γ -33-P]-Adenosine Triphosphate into a test substrate (GST-Retinoblastoma). In each well was placed the compound to be tested (diluted in DMSO and water to correct concentrations)
20 and in control wells either p16 as an inhibitor control or DMSO as a positive control.

Approximately 0.5 μ l of CDK4/Cyclin D1 partially-purified enzyme (amount dependent on enzyme activity) diluted in 25 μ l incubation buffer was added to each well then 20 μ l of GST-Rb/ATP/ATP33 mixture (containing 0.5 μ g GST-Rb and 0.2 μ M ATP and 0.14 μ Ci [γ -33-P]-Adenosine Triphosphate), and the resulting mixture shaken gently, then
25 incubated at room temperature for 60 minutes.

To each well was then added 150 μ L stop solution containing (0.8mg/well of Protein A-PVT SPA bead (Amersham)), 20pM/well of Anti-Glutathione Transferase, Rabbit IgG (obtained from Molecular Probes), 61mM EDTA and 50mM HEPES pH 7.5 containing 0.05% sodium azide.

30 The plates were sealed with Topseal-S plate sealers, left for two hours then spun at 2500rpm, 1124xg., for 5 minutes. The plates were read on a Topcount for 30 seconds per well.

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The incubation buffer used to dilute the enzyme and substrate mixes contained 50mM HEPES pH7.5, 10mM MnCl₂, 1mM DTT, 100µM Sodium vanadate, 100µM NaF, 10mM Sodium Glycerophosphate, BSA (1mg/ml final).

As a control, another known inhibitor of CDK4 may be used in place of p16.

5 Test substrate

In this assay only part of the retinoblastoma (Science 1987 Mar13;235 (4794):1394-1399; Lee W.H., Bookstein R., Hong F., Young L.J., Shew J.Y., Lee E.Y.) was used, fused to a GST tag. PCR of retinoblastoma amino acids 379-928 (obtained from retinoblastoma plasmid ATCC pLRbRNL) was performed, and the sequence cloned into
10 pGEX 2T fusion vector (Smith D.B. and Johnson, K.S. Gene 67, 31 (1988); which contained a tac promoter for inducible expression, internal lac I^q gene for use in any E.Coli host. and a coding region for thrombin cleavage -obtained from Pharmacia Biotech) which was used to amplify amino acids 792-928. This sequence was again cloned into pGEX 2T.

The retinoblastoma 792-928 sequence so obtained was expressed in E.Coli (BL21
15 (DE3) pLysS cells) using standard inducible expression techniques, and purified as follows.

E.coli paste was resuspended in 10ml/g of NETN buffer (50mM Tris pH 7.5, 120mM NaCl, 1mM EDTA, 0.5%v/v NP-40, 1mM PMSF, 1ug/ml leupeptin, 1ug/ml aprotinin and 1ug/ml pepstatin) and sonicated for 2 x 45 seconds per 100ml homogenate. After centrifugation, the supernatant was loaded onto a 10ml glutathione Sepharose column
20 (Pharmacia Biotech, Herts, UK), and washed with NETN buffer. After washing with kinase buffer (50mM HEPES pH 7.5, 10mM MgCl₂, 1mM DTT, 1mM PMSF, 1ug/ml leupeptin, 1ug/ml aprotinin and 1ug/ml pepstatin) the protein was eluted with 50mM reduced glutathione in kinase buffer. Fractions containing GST-Rb(792-927) were pooled and dialysed overnight against kinase buffer. The final product was analysed by Sodium Dodeca Sulfate
25 (SDS) PAGE (Polyacrylamide gel) using 8-16% Tris-Glycine gels (Novex, San Diego, USA).
CDK4 and Cyclin D1

CDK4 and Cyclin D1 were cloned from RNA from MCF-7 cell line (obtained from ATCC number:HTB22, breast adenocarcinoma line) as follows. The RNA was prepared from MCF-7 cells, then reverse transcribed using oligo dT primers. PCR was used to amplify the
30 complete coding sequence of each gene [CDK4 amino acids 1-303; Ref. Cell 1992 Oct 16; 71 (2): 323-334; Matsushime H., Ewen M.E., Stron D.K., Kato J.Y., Hanks S.K., Roussel M.F., Sherr C.J. and Cyclin D1 amino acids 1-296; Ref. Cold Spring Harb. Symp. Quant. Biol.,

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1991; 56:93-97; Arnold A., Motokura T., Bloom T., Kronenburg, Ruderman J., Juppner H., Kim H.G.].

After sequencing the PCR products were cloned using standard techniques into the insect expression vector pVL1393 (obtained from Invitrogen 1995 catalogue number :

5 V1392-20). The PCR products were then dually expressed [using a standard virus Baculogold co-infection technique] into the insect SF21 cell system (Spodoptera Frugiperda cells derived from ovarian tissue of the Fall Army Worm -commercially available).

The following Example provides details of the production of Cyclin D1/CDK4 in SF21 cells (in TC100 + 10% FBS(TCS) + 0.2% Pluronic) having dual infection MOI 3 for
10 each virus of Cyclin D1 & CDK4.

Example production of Cyclin D1/CDK4

SF21 cells grown in a roller bottle culture to 2.33×10^6 cells/ml were used to inoculate 10 x 500 ml roller bottles at 0.2×10^6 cells/ml. The roller bottles were incubated on a roller rig at 28°C.

15 After 3 days (72 hrs.) the cells were counted, and the average from 2 bottles found to be 1.86×10^6 cells/ml. (99% viable). The cultures were then infected with the dual viruses at an MOI 3 for each virus.

10 x 500ml were infected with JS303 Cyclin D1 virus titre -9×10^7 pfu/ml. JS304 CDK4 virus titre -1×10^8 pfu/ml.

20 Cyclin D1 $\frac{1.86 \times 10^6 \times 500 \times 3}{0.9 \times 10^8} = 31$ ml of virus for each 500 ml. bottle.

CDK4 $\frac{1.86 \times 10^6 \times 500 \times 3}{1 \times 10^8} = 28$ ml of virus for each 500 ml. bottle.

25 The viruses were mixed together before addition to the cultures, and the cultures returned to the roller rig 28°C.

After 3 days (72 hrs.) post infection the 5 Litres of culture was harvested. The total cell count at harvest was 1.58×10^6 cells/ml.(99% viable). The cells were spun out at 2500rpm, 30 mins., 4°C in Heraeus Omnifuge 2.0 RS in 250 mls. lots. The supernatant was
30 discarded.

20 pellets of $\sim 4 \times 10^8$ cells/pellet were snap frozen in LN₂ and stored at -80°C in CCRF cold room. The SF21 cells were then hypotonically lysed by resuspending in lysis buffer

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(50mM HEPES pH 7.5, 10mM magnesium chloride, 1mM DTT, 10mM glycerophosphate, 0.1mM PMSF, 0.1mM sodium fluoride, 0.1mM sodium orthovanadate, 5ug/ml aprotinin, 5ug/ml leupeptin and 20% w/v sucrose), and adding ice cold deionised water. After centrifugation, the supernatant was loaded onto a Poros HQ/M 1.4/100 anion exchange

5 column (PE Biosystems, Hertford, UK). CDK4 and Cyclin D1 were coeluted with 375mM NaCl in lysis buffer, and their presence checked by western blot, using suitable anti-CDK4 and anti-Cyclin D1 antibodies (obtained from Santa Cruz Biotechnology, California, US).
p16 control (Nature 366.:704-707; 1993; Serrano M, Hannon GJ, Beach D)

p16 (the natural inhibitor of CDK4/Cyclin D1) was amplified from HeLa cDNA (Hela
10 cells obtained from ATCC CCL2, human epitheloid carcinoma from cervix; Cancer Res. 12: 264. 1952), cloned into pTB 375 NBSE which had a 5' His tag, and transformed using standard techniques into BL21 (DE3) pLysS cells (obtained from Promega; Ref. Studier F.W. and Moffat B.A., J. Mol. Biol., 189, 113, 1986). A 1 litre culture was grown to the appropriate OD then induced with IPTG to express p16 overnight. The cells were then lysed by sonication
15 in 50mM sodium phosphate, 0.5M sodium chloride, PMSF, 0.5µg/ml leupeptin and 0.5µg/ml aprotinin. The mixture was spun down, the supernatant added to nickel chelate beads and mixed for 1 ½ hours. The beads were washed in sodium phosphate, NaCl pH 6.0 and p16 product eluted in sodium phosphate, NaCl pH 7.4 with 200mM imidazole.

The pTB NBSE was constructed from pTB 375 NBPE as follows :-

20 pTB375

The background vector used for generation of pTB 375 was pZEN0042 (see UK patent 2253852) and contained the tetA/tetR inducible tetracycline resistance sequence from plasmid RP4 and the cer stability sequence from plasmid pKS492 in a pAT153 derived background. pTB375 was generated by the addition of an expression cassette consisting of the T7 gene 10
25 promoter, multiple cloning site and T7 gene 10 termination sequence. In addition, a terminator sequence designed to reduce transcriptional readthrough from the background vector was included upstream of the expression cassette.

pTB 375 NBPE

The unique EcoRI restriction site present in pTB 375 was removed. A new multiple
30 cloning site containing the recognition sequences for the restriction enzymes NdeI, BamHI, PstI and EcoRI was introduced into pTB 375 between the NdeI and BamHI sites destroying the original BamHI site present in pTB 375.

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pTB 375 NBSE

A new multiple cloning site containing the recognition sequences for the restriction enzymes NdeI, BamHI, SmaI and EcoRI was introduced into pTB 375 NBPE between the NdeI and EcoRI sites. The oligonucleotide containing these restriction sites also contained 6
5 histidine codons located between the NdeI and BamHI sites in the same reading frame as the initiator codon (ATG) present within the NdeI site.

By analogy, assays designed to assess inhibition of CDK2 and CDK6 may be constructed.

Although the pharmacological properties of the compounds of the formula (I) vary
10 with structural change, in general activity possessed by compounds of the formula (I) may be demonstrated at IC_{50} concentrations or doses in the range 250 μ M to 1 nM.

When tested in the above *in vitro* assay the CDK4 inhibitory activity of Example 6 was measured as $IC_{50} = 1.2 \mu$ M.

According to a further aspect of the invention there is provided a pharmaceutical
15 composition which comprises a pyrimidine derivative of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in association with a pharmaceutically acceptable diluent or carrier.

The composition may be in a form suitable for oral administration, for example as a tablet or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular,
20 intravascular or infusion) as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository.

In general the above compositions may be prepared in a conventional manner using conventional excipients.

The pyrimidine will normally be administered to a warm-blooded animal at a unit dose
25 within the range 5-5000 mg per square meter body area of the animal, i.e. approximately 0.1-100 mg/kg, and this normally provides a therapeutically-effective dose. A unit dose form such as a tablet or capsule will usually contain, for example 1-250 mg of active ingredient. Preferably a daily dose in the range of 1-50 mg/kg is employed. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration,
30 and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

According to a further aspect of the present invention there is provided a pyrimidine

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derivative of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore for use in a method of treatment of the human or animal body by therapy.

We have found that the pyrimidine derivatives defined in the present invention, or a
5 pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, are effective cell cycle inhibitors (anti-cell proliferation agents), which property is believed to arise from their CDK inhibitory properties. Accordingly the compounds of the present invention are expected to be useful in the treatment of cell-cycle (proliferative) diseases or medical conditions, for example those mediated alone or in part by CDK enzymes, i.e. the compounds may be used to produce
10 a CDK inhibitory effect in a warm-blooded animal in need of such treatment. Thus the compounds of the present invention provide a method for treating the proliferation of malignant cells, for example, characterised by inhibition of CDK enzymes, i.e. the compounds may be used to produce an anti-proliferative effect mediated alone or in part by the inhibition of CDKs. Such a pyrimidine derivative of the invention is expected to possess a wide range of
15 anti-cancer properties as CDKs have been implicated in many common human cancers such as leukaemia and breast, lung, colon, rectal, stomach, prostate, bladder, pancreas and ovarian cancer. Thus it is expected that a pyrimidine derivative of the invention will possess anti-cancer activity against these cancers. It is in addition expected that a pyrimidine derivative of the present invention will possess activity against a range of leukaemias,
20 lymphoid malignancies and solid tumours such as carcinomas and sarcomas in tissues such as the liver, kidney, prostate and pancreas. In particular such compounds of the invention are expected to slow advantageously the growth of primary and recurrent solid tumours of, for example, the colon, breast, prostate, lungs and skin. More particularly such compounds of the invention, or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, are
25 expected to inhibit the growth of those primary and recurrent solid tumours which are associated with CDKs, especially those tumours which are significantly dependent on CDKs for their growth and spread, including for example, certain tumours of the colon, breast, prostate, lung, vulva and skin.

It is further expected that a pyrimidine derivative of the present invention will possess
30 activity against other cell-proliferation diseases in a wide range of other disease states including leukemias, fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma,

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atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation.

Thus according to this aspect of the invention there is provided a pyrimidine derivative of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore for use as a medicament; and the use of a pyrimidine derivative of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in the manufacture of a medicament for use in the production of a cell cycle inhibitory (anti-cell-proliferation) effect in a warm-blooded animal such as man. Particularly, an inhibitory effect is produced at the S- or G1-S phase by inhibition of CDK2, CDK4 and/or CDK6, especially CDK4 and CDK6.

According to a further feature of this aspect of the invention there is provided a method for producing a cell cycle inhibitory (anti-cell-proliferation) effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a pyrimidine derivative as defined immediately above. Particularly, an inhibitory effect is produced at the S- or G1-S phase by inhibition of CDK2, CDK4 and/or CDK6, especially CDK4 and CDK6.

As stated above the size of the dose required for the therapeutic or prophylactic treatment of a particular cell-proliferation disease will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated. A unit dose in the range, for example, 1-100 mg/kg, preferably 1-50 mg/kg is envisaged.

The cell-cycle, CDK inhibitory, activity defined hereinbefore may be applied as a sole therapy or may involve, in addition to a compound of the invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. In the field of medical oncology it is normal practice to use a combination of different forms of treatment to treat each patient with cancer. In medical oncology the other component(s) of such conjoint treatment in addition to the cell cycle inhibitory treatment defined hereinbefore may be: surgery, radiotherapy or chemotherapy. Such chemotherapy may cover three main categories of therapeutic agent:

(i) other cell cycle inhibitory agents that work by the same or different mechanisms from those defined hereinbefore;

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- (ii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene, idoxifene), progestogens (for example megestrol acetate), aromatase inhibitors (for example anastrozole, letrozole, vorazole, exemestane), antiprogestogens, antiandrogens (for example flutamide, nilutamide, bicalutamide, cyproterone acetate), LHRH agonists and
5 antagonists (for example goserelin acetate, luprolide), inhibitors of testosterone
5 α -dihydroreductase (for example finasteride), anti-invasion agents (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function) and inhibitors of growth factor function, (such growth factors include for example platelet derived growth factor and hepatocyte growth factor such inhibitors include
10 growth factor antibodies, growth factor receptor antibodies, tyrosine kinase inhibitors and serine/threonine kinase inhibitors); and
- (iii) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as antimetabolites (for example antifolates like methotrexate, fluoropyrimidines like 5-fluorouracil, purine and adenosine analogues, cytosine arabinoside);
15 antitumour antibiotics (for example anthracyclines like doxorubicin, daunomycin, epirubicin and idarubicin, mitomycin-C, dactinomycin, mithramycin); platinum derivatives (for example cisplatin, carboplatin); alkylating agents (for example nitrogen mustard, melphalan, chlorambucil, busulphan, cyclophosphamide, ifosfamide, nitrosoureas, thiotepa); antimetotic agents (for example vinca alkaloids like vincristine and taxoids like taxol, taxotere);
20 topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan). According to this aspect of the invention there is provided a pharmaceutical product comprising a pyrimidine derivative of the formula (I) as defined hereinbefore and an additional anti-tumour substance as defined hereinbefore for the conjoint treatment of cancer. An anti-emetic may also be usefully administered, for example when
25 using such conjoint treatment as described above.

In addition to their use in therapeutic medicine, the compounds of formula (I) and their pharmaceutically acceptable salts are also useful as pharmacological tools in the development and standardisation of *in vitro* and *in vivo* test systems for the evaluation of the effects of inhibitors of cell cycle activity in laboratory animals such as cats, dogs, rabbits,
30 monkeys, rats and mice, as part of the search for new therapeutic agents.

In the above other, pharmaceutical composition, process, method, use and medicament manufacture features, the alternative and preferred embodiments of the compounds of the

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invention described herein also apply.

The invention will now be illustrated in the following non-limiting Examples, in which standard techniques known to the skilled chemist and techniques analogous to those described in these Examples may be used where appropriate, and in which, unless otherwise

5 stated:-

(i) evaporations were carried out by rotary evaporation in vacuo and work-up procedures

were carried out after removal of residual solids such as drying agents by filtration;

(ii) operations were carried out at ambient temperature, typically in the range 18-25°C and in air unless stated, or unless the skilled person would otherwise operate under an atmosphere of

10 an inert gas such as argon;

(iii) column chromatography (by the flash procedure) and medium pressure liquid

chromatography (MPLC) were performed on Merck Kieselgel silica (Art. 9385) or Merck

Lichroprep RP-18 (Art. 9303) reversed-phase silica obtained from E. Merck, Darmstadt, Germany;

15 (iv) yields are given for illustration only and are not necessarily the maximum attainable;

(v) melting points where given were determined using a Mettler SP62 automatic melting point apparatus, an oil-bath apparatus or a Koffler hot plate apparatus.

(vi) the structures of the end-products of the formula (I) were generally confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral techniques; proton magnetic

20 resonance chemical shift values were measured in deuterated DMSO-d₆ (unless otherwise stated) on the delta scale (ppm downfield from tetramethylsilane) using a Varian Gemini 2000

spectrometer operating at a field strength of 300MHz, or a Bruker AM250 spectrometer

operating at a field strength of 250MHz; and peak multiplicities are shown as follows: s,

singlet; d, doublet; t, triplet; m, multiplet; br, broad; mass spectrometry (MS) was performed

25 by electrospray on a VG platform;

(vii) where the Examples below possess chiral centres a racemic mixture is obtained unless otherwise stated;

(viii) intermediates were not generally fully characterised and purity was assessed by thin layer chromatography (TLC), high performance liquid chromatography (HPLC), infra-red

30 (IR), MS or NMR analysis;

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(ix) the following abbreviations may be used hereinbefore or hereinafter :-

DMF *N,N*-dimethylformamide; and

DMSO dimethylsulphoxide.

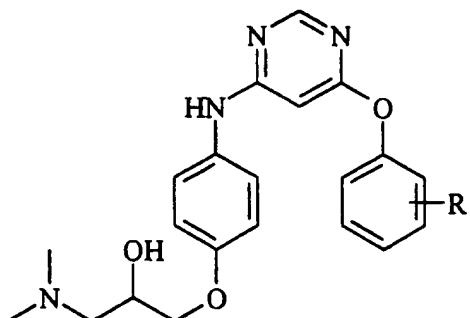
5 Example 1

4-(2-Bromo-4-methylphenoxy)-6-{4-[3-(*N,N*-dimethyl)amino-2-hydroxy-propoxy]anilino}pyrimidine

A mixture of 4-(2-bromo-4-methylphenoxy)-6-chloropyrimidine (Reference Example 2, 550mg) and 4-[3-(*N,N*-dimethyl)amino-2-hydroxy-propoxy]aniline (Reference Example 1, 436mg) was heated to 60°C in *n*-butanol (10 ml), sufficient methanol (ca. 5 ml) was added to effect a solution, the reaction temperature raised to reflux, and stirred for 16 hours. Silica gel (1 g) was added to the reaction mixture, after cooling 7M ammonia in methanol (10 ml) was added and the mixture adsorbed onto the silica and purified by column chromatography, eluting with 10% 7M methanolic ammonia/dichloromethane, to yield the title compound as a solid (130mg, 17%). NMR: 2.2 (6H, s), 2.3-2.5 (5H, m), 3.8-4.0 (3H, m), 4.8 (1H, br s), 5.9 (1H, s), 6.9 (2H, m), 7.1-7.3 (2H, m), 7.4-7.5 (2H, m), 7.6 (1H, m), 8.2 (1H, s), 9.35; MS: (electrospray) 474 (MH)⁺.

Examples 2-11:

The following compounds were prepared by the method of Example 1 using the appropriate phenoxypyrimidine (prepared by analogy to Reference Example 2) and 4-[3-(*N,N*-dimethyl)amino-2-hydroxy-propoxy]aniline (Reference Example 1) :



Ex	R ¹	NMR	M.S. (MH ⁺)	Yield (%)
2	H	2.2 (6H, s), 2.2-(1H, m), 2.4 (1H, m), 3.75-4.0 (3H, m), 4.7 (1H, br s), 5.9 (1H, s), 6.85 (2H, m), 7.1 (2H, m), 7.3 (1H, m), 7.4 (4H, m) 8.25 (1H, s), 9.3 (1H, s)	382.5	16
3	2-Cl 5-Me	2.2 (6H, s), 2.2-2.4 (5H, m), 3.75-4.0 (3H, m), 4.7 (1H, br s), 6.05 (1H, m), 6.85 (2H, m), 7.15 (2H, m) 7.4 (4H, m) 8.25 (1H, s), 9.4 (1H, s)	429.5	22
4	2-MeO	2.2 (6H, s), 2.3 (1H, m), 2.4 (1H, m), 3.75 (3H, s), 3.8-4.0 (3H, m), 4.8 (1H, br s), 5.9 (1H, s), 6.85 (2H, m), 7.0 (1H, m), 7.15 (2H, m), 7.35 (1H, m), 7.4 (3H, m) 8.25 (1H, s), 9.3 (1H, s)	410	27
5	2-CF ₃	2.2 (6H, s), 2.3 (1H, m), 2.4 (1H, m), 3.8-4.0 (3H, m), 4.8 (1H, br s), 6.1 (1H, s), 6.85 (2H, m), 7.0 (1H, m), 7.15 [*] (2H, m), 7.35 (1H, m), 7.4 (3H, m) 8.25 (1H, s), 9.4 (1H, s)	449.5	74
6	2,5-di-Me	2.1 (3H, s) 2.2 (6H, s), 2.2-2.4 (5H, m), 3.75-4.0 (3H, m), 4.7 (1H, br s), 5.9 (1H, s), 6.85 (2H, m), 7.1 (2H, m), 7.3 (1H, m), 7.4 (2H, m) 8.25 (1H, s), 9.3 (1H, s)	409.5	19
7	3-MeO	2.2 (6H, s), 2.3 (1H, m), 2.4 (1H, m), 3.75 (3H, s), 3.8-4.0 (3H, m), 4.8 (1H, br s), 5.9 (1H, s), 6.75 (1H, m), 6.9 (2H, m), 7.35 (3H, m), 8.25 (1H, s), 9.3 (1H, s)	410	33
8	3-CF ₃	2.2 (6H, s), 2.3 (1H, m), 2.4 (1H, m), 3.8-4.0 (3H, m), 4.8 (1H, br s), 6.1 (1H, s), 6.85 (2H, m), 7.35-7.8 (6H, m) 8.25 (1H, s), 9.4 (1H, s)	448	21
9	4-MeO	2.2 (6H, s), 2.3 (1H, m), 2.4 (1H, m), 3.75 (3H, s), 3.8-4.0 (3H, m), 4.8 (1H, br s), 5.9 (1H, s), 6.75 (2H, d), 7.0 (2H, d), 7.1 (2H, d), 8.25 (1H, s), 9.3 (1H, s)	410	31
10	4-CF ₃	2.2 (6H, s), 2.3 (1H, m), 2.4 (1H, m), 3.8-4.0 (3H, m), 4.8 (1H, br s), 5.9 (1H, s), 6.85 (2H, d), 7.4 (4H, m), 7.8 (2H,	447	20

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		d), 8.25 (1H, s), 9.4 (1H, s)		
11	2,5-di-Cl	2.2 (6H, s), 2.2-(1H, m), 2.4 (1H, m), 3.75-4.0 (3H, m), 4.7 (1H, br s), 6.1 (1H, s), 6.85 (2H, m), 7.3-7.5 (3H, m), 7.55-7.85 (2H, m), 8.25 (1H, s), 9.4 (1H, s)	449	9

Preparation of Starting Materials

The starting materials for the Examples above are either commercially available or are readily prepared by standard methods from known materials. For example, the following
 5 reactions are an illustration, but not a limitation, of some of the starting materials used in the above reactions.

Reference Example 1**4-[3-(*N,N*-Dimethyl)amino-2-hydroxy-propoxy]aniline**

10 3-(*N,N*-Dimethyl)amino-2-hydroxy-3-(4-nitrophenoxy)propane (Reference Example 1-A, 3.75 g) was dissolved in ethanol (40 ml). Under an atmosphere of nitrogen, 10% palladium-on-carbon (0.4g) was added. The nitrogen atmosphere was replaced by one of hydrogen and the reaction mixture was stirred overnight. The catalyst was removed by
 filtration through diatomaceous earth and the filtrate was evaporated to dryness. The residue
 15 was dissolved in diethyl ether containing a small amount of isopropanol and hydrogen chloride solution (1M in ether, 16 ml) was added. The ether was evaporated and the solid residue was suspended in isopropanol. This mixture was heated on a steam bath for several minutes then allowed to cool to ambient temperature. The resulting powder was collected by
 filtration, washed with isopropanol, ether and dried (3.04 g 72.4%). NMR (300 MHz): 2.80 (s,
 20 6H), 3.15 (m, 2H), 3.88 (m, 2H), 4.25 (m, 1H), 5.93 (br s, 1H), 6.88 (m, 4H); M.S.: (ES⁺) 211 (MH⁺); C₁₁H₁₈N₂O₂ · 1.6 HCl requires C; 49.2, H; 7.4, N; 10.4, Cl; 21.7%; found: C; 49.2, H; 7.2, N; 10.1; Cl; 19.1%.

Reference Example 1-A**25 3-(*N,N*-Dimethyl)amino-2-hydroxy-1-(4-nitrophenoxy)propane**

1-(4-Nitrophenoxy)-2,3-epoxypropane (Reference Example 1-B, 4.3 g) was dissolved in methanol (30 ml) and DMF (10 ml). Dimethylamine (2M solution in methanol, 17 ml) was added and the mixture was stirred at ambient temperature overnight. The reaction mixture was

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evaporated to dryness and the residue was dissolved in saturated sodium bicarbonate solution and ethyl acetate. The ethyl acetate layer was separated and washed twice with saturated brine, dried over anhydrous sodium sulphate, filtered and evaporated to yield an oil that slowly crystallised under high vacuum (4.79g, 89.9%). NMR: (CDCl₃, 300 MHz) 2.33 (s, 6H), 2.98 (m, 1H), 2.54 (m, 1H), 4.00 (m, 3 H), 7.00 (d, 2H), 8.20 (d, 2H); M.S.: (ES⁺) 241 (MH⁺).

Reference Example 1-B

1-(4-Nitrophenoxy)-2,3-epoxypropane

10 1-(4-Nitrophenoxy)-2,3-epoxypropane was prepared by an analogous method to that described by Zhen-Zhong Lui *et. al.* in Synthetic Communications (1994), 24, 833-838.

4-Nitrophenol (4.0 g), anhydrous potassium carbonate (8.0 g) and tetrabutylammonium bromide (0.4 g) were mixed with epibromohydrin (10 ml). The reaction mixture was heated at 100°C for 1 hour. After cooling to ambient temperature, the reaction mixture was diluted with ethyl acetate and filtered. The filtrate was evaporated to dryness and the residue was co-distilled twice with toluene. The resulting oil was purified by column chromatography and eluted with ethanol (1.0%):dichloromethane to yield on evaporation an oil that crystallised (4.36 g, 77.7%). NMR: (CDCl₃, 300 MHz) 2.78 (m, 1H), 2.95 (m, 1H), 3.38 (m, 1H), 4.02 (dd, 1 H), 4.38 (dd, 1H), 7.00 (d, 2H), 8.20 (d, 2H); M.S.: (ES⁺) 196 (MH⁺).

Reference Example 2

4-(2-Bromo-4-methylphenoxy)-6-chloropyrimidine

To a solution of 2-bromo-4-methylphenol (500mg), in dimethyl sulphoxide (2 ml), was added freshly ground potassium carbonate (407mg). The mixture was stirred for 20 minutes, and 4,6-dichloropyrimidine (432mg) was added. The mixture was stirred at ambient temperature for 2 hours, and the reaction mixture preadsorbed onto silica gel (1g) and purified by column chromatography (eluting with 10% ethyl acetate/dichloromethane) to yield a gum (571mg, 71%). NMR: 2.35 (3H, s), 7.25 (2H, s), 7.5 (1H, s), 7.55 (1H, s), 8.7 (1H, s); MS: (electrospray) 451 (MH⁺).

Example 12

The following illustrate representative pharmaceutical dosage forms containing the compound of formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof (hereafter compound X), for therapeutic or prophylactic use in humans:-

5

(a): Tablet I	mg/tablet
Compound X	100
Lactose Ph.Eur	182.75
Croscarmellose sodium	12.0
Maize starch paste (5% w/v paste)	2.25
Magnesium stearate	3.0

(b): Tablet II	mg/tablet
Compound X	50
Lactose Ph.Eur	223.75
Croscarmellose sodium	6.0
Maize starch	15.0
Polyvinylpyrrolidone (5% w/v paste)	2.25
Magnesium stearate	3.0

(c): Tablet III	mg/tablet
Compound X	1.0
Lactose Ph.Eur	93.25
Croscarmellose sodium	4.0
Maize starch paste (5% w/v paste)	0.75
Magnesium stearate	1.0

(d): Capsule	mg/capsule
Compound X	10
Lactose Ph.Eur	488.5

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Magnesium stearate	1.5
--------------------	-----

(e): Injection I	(50 mg/ml)
Compound X	5.0% w/v
1M Sodium hydroxide solution	15.0% v/v
0.1M Hydrochloric acid	(to adjust pH to 7.6)
Polyethylene glycol 400	4.5% w/v
Water for injection	to 100%

(f): Injection II	10 mg/ml
Compound X	1.0% w/v
Sodium phosphate BP	3.6% w/v
0.1M Sodium hydroxide solution	15.0% v/v
Water for injection	to 100%

(g): Injection III	(1mg/ml,buffered to pH6)
Compound X	0.1% w/v
Sodium phosphate BP	2.26% w/v
Citric acid	0.38% w/v
Polyethylene glycol 400	3.5% w/v
Water for injection	to 100%

5 Note

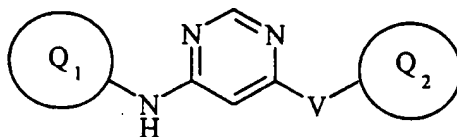
The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.

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CLAIMS

What we claim is:

1. A pyrimidine derivative of the formula (I):

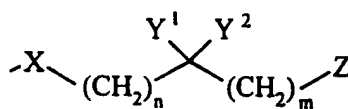


(I)

wherein

V is O or S;

- Q₁ and Q₂ are independently selected from phenyl, naphthyl, a 5-or 6-membered monocyclic moiety (linked via a ring carbon atom and containing one to three heteroatoms independently selected from nitrogen, oxygen and sulphur); and a 9-or 10-membered bicyclic heterocyclic moiety (linked via a ring carbon atom and containing one or two nitrogen heteroatoms and optionally containing a further one or two heteroatoms selected from nitrogen, oxygen and sulphur); provided that there is an available carbon atom in Q₁ such that the substituent of formula (Ia) (defined hereinbelow) is not adjacent to the -NH-link; and Q₁ is substituted on an available carbon atom not adjacent to the -NH-link one substituent of the formula (Ia), and Q₂ may optionally bear on any available carbon atom further substituents of the formula (Ia):



(Ia)

wherein:

X is -CH₂-, -O-, -NH-, -NR^r- or -S- [wherein R^r is C₁₋₄alkyl, optionally substituted by one substituent selected from halo, amino, cyano, C₁₋₄alkoxy or hydroxy];

Y¹ is H, C₁₋₄alkyl or as defined for Z;

- 25 Y² is H or C₁₋₄alkyl;

Z is R^aO-, R^bR^cN-, R^dS-, R^eR^fNNR^g-, a nitrogen linked heteroaryl or a nitrogen linked heterocycle [wherein said heterocycle is optionally substituted on a ring carbon or a ring nitrogen by C₁₋₄alkyl or C₁₋₄alkanoyl] wherein R^a, R^b, R^c, R^d, R^e, R^f and R^g are independently

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selected from hydrogen, C₁₋₄alkyl, C₂₋₄alkenyl, C₃₋₃cycloalkyl, and wherein said C₁₋₄alkyl and C₂₋₄alkenyl are optionally substituted by one or more phenyl;

n is 1, 2 or 3;

m is 1, 2 or 3;

- 5 and Q₁ and Q₂ may optionally and independently bear on any available carbon atom up to four substituents independently selected from halo, hydroxy, thio, nitro, carboxy, cyano, C₂₋₄alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent], C₂₋₄alkynyl, C₁₋₃alkanoyl, C₁₋₄alkoxycarbonyl, C₁₋₄alkyl, hydroxy-C₁₋₃alkyl, fluoro-C₁₋₄alkyl, amino-C₁₋₃alkyl, C₁₋₄alkylamino-C₁₋₃alkyl, *N,N*-di-(C₁₋₄alkyl)amino-C₁₋₃alkyl, 10 cyano-C₁₋₄alkyl, C₂₋₄alkanoyloxy-C₁₋₄alkyl, C₁₋₄alkoxy-C₁₋₃alkyl, carboxy-C₁₋₄alkyl, C₁₋₄alkoxycarbonyl-C₁₋₄alkyl, carbamoyl-C₁₋₄alkyl, *N*-C₁₋₄alkylcarbamoyl-C₁₋₄alkyl, *N,N*-di-(C₁₋₄alkyl)-carbamoyl-C₁₋₄alkyl, pyrrolidin-1-yl-C₁₋₃alkyl, piperidin-1-yl-C₁₋₃alkyl, piperazin-1-yl-C₁₋₃alkyl, morpholino-C₁₋₃alkyl, thiomorpholino-C₁₋₃alkyl, piperazin-1-yl, morpholino, thiomorpholino, C₁₋₄alkoxy, cyano-C₁₋₄alkoxy, carbamoyl-C₁₋₄alkoxy, 15 *N*-C₁₋₄alkylcarbamoyl-C₁₋₄alkoxy, *N,N*-di-(C₁₋₄alkyl)-carbamoyl-C₁₋₄alkoxy, 2-aminoethoxy, 2-C₁₋₄alkylaminoethoxy, 2-*N,N*-di-(C₁₋₄alkyl)aminoethoxy, C₁₋₄alkoxycarbonyl-C₁₋₄alkoxy, halo-C₁₋₄alkoxy, 2-hydroxyethoxy, C₂₋₄alkanoyloxy-C₂₋₄alkoxy, 2-C₁₋₄alkoxyethoxy, carboxy-C₁₋₄alkoxy, C₃₋₃alkenyloxy, C₃₋₃alkynyloxy, C₁₋₄alkylthio, C₁₋₄alkylsulphinyl, C₁₋₄alkylsulphonyl, ureido (H₂N-CO-NH-), C₁₋₄alkylNH-CO-NH-, 20 *N,N*-di-(C₁₋₄alkyl)N-CO-NH-, C₁₋₄alkylNH-CO-N(C₁₋₄alkyl)-, *N,N*-di-(C₁₋₄alkyl)N-CO-N(C₁₋₄alkyl)-, carbamoyl, *N*-(C₁₋₄alkyl)carbamoyl, *N,N*-di-(C₁₋₄alkyl)carbamoyl, amino, C₁₋₄alkylamino, *N,N*-di-(C₁₋₄alkyl)amino, C₂₋₄alkanoylamino,

- and also independently, or in addition to, the above optional substituents, Q₁ and Q₂ 25 may optionally and independently bear on any available carbon atom up to two further substituents independently selected from phenyl-C₁₋₄alkyl, phenyl-C₁₋₄alkoxy, phenyl, naphthyl, benzoyl and a 5-or 6-membered aromatic heterocycle (linked via a ring carbon atom and containing one to three heteroatoms independently selected from oxygen, sulphur and nitrogen); wherein said naphthyl, phenyl, benzoyl, 5-or 6-membered aromatic heterocyclic 30 substituents and the phenyl group in said phenyl-C₁₋₄alkyl and phenyl-C₁₋₄alkoxy substituents may optionally bear one or two substituents independently selected from halo, C₁₋₄alkyl and C₁₋₄alkoxy;

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or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

2. A pyrimidine derivative according to claim 1 wherein Q₁ and Q₂ are phenyl, or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

5

3. A pyrimidine derivative according to claims 1 or 2 wherein V is O, or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

4. A pyrimidine derivative according to any one of claims 1 to 3 wherein the substituent
10 of formula (Ia) is 3-dimethylamino-2-hydroxypropoxy, or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

5. A pyrimidine derivative according to any one of claims 1 to 4 wherein the substituent
of formula (Ia) is on Q₁; or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester
15 thereof.

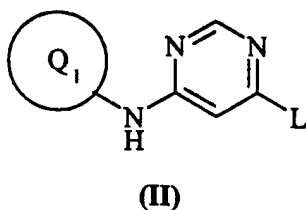
6. A pyrimidine derivative according to any one of claims 1 to 5 wherein Q₂ is optionally
substituted by one or two groups selected from chloro, bromo, methoxy, methyl or
trifluoromethyl; or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

20

7. A pyrimidine derivative according to any one of claims 1 to 6 which is:
4-{4-[2-hydroxy-3-(*N,N*-dimethylamino)propoxy]anilino}-2-(2,5-dimethylphenoxy)
pyrimidine; or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

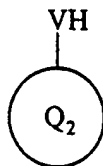
25 8. A process for preparing a pyrimidine derivative of the formula (I) which comprises
of:-

a) reacting a pyrimidine of formula (II):



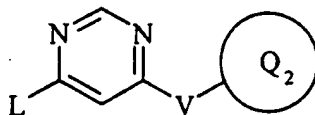
- 44 -

wherein L is a displaceable group, with a compound of formula (III):



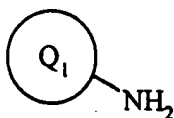
(III)

b) reaction of a pyrimidine of formula (IV):



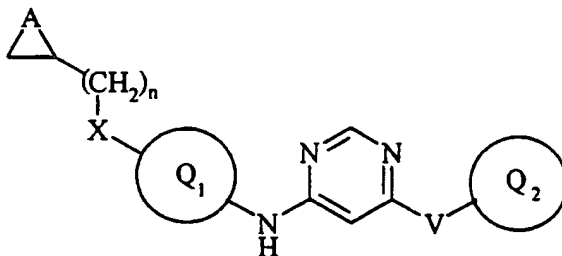
(IV)

wherein L is a displaceable group, with a compound of formula (V):



(V)

10 c) for compounds of formula (I) where $m = 1$ and Y is OH, NH₂ or SH, reaction of a 3-membered heteroalkyl ring of formula (VI):



(VI)

wherein A is O, S or NH;

15 with a nucleophile of formula (VII):

Z-D

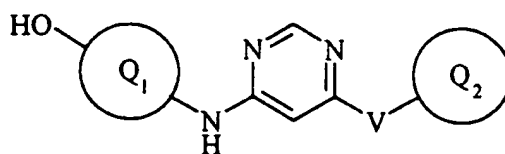
(VII)

wherein D is H or a suitable counter-ion;

d) for compounds of formula (I) where X is oxygen, by reaction of an alcohol of formula

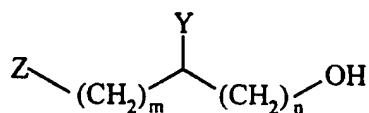
20 (VIII):

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(VIII)

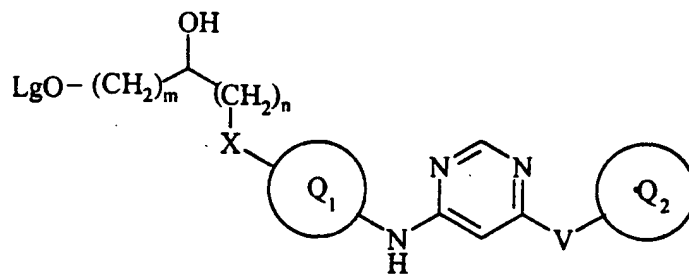
with an alcohol of formula (IX):



(IX)

5

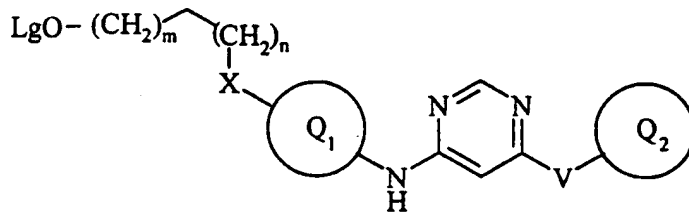
e) for compounds of formula (I) wherein X is $-\text{CH}_2-$, $-\text{O}-$, $-\text{NH}-$ or $-\text{S}-$, Y^1 is OH, Y^2 is H and m is 2 or 3; reaction of a compound of formula (X):



(X)

10 wherein LgO is a leaving group; with a nucleophile of formula (VII);

f) for compounds of formula (I) wherein X is $-\text{CH}_2-$, $-\text{O}-$, $-\text{NH}-$ or $-\text{S}-$; Y^1 and Y^2 are H; n is 1, 2 or 3 and m is 1, 2 or 3; reaction of a compound of formula (XI):

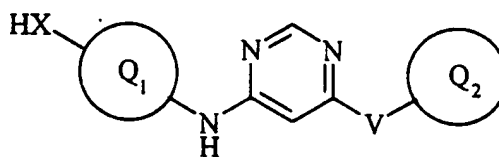


(XI)

15 wherein LgO is a leaving group; with a nucleophile of formula (VII);

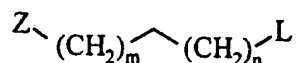
g) for compounds of formula (I) wherein X is $-\text{O}-$, $-\text{NH}-$ or $-\text{S}-$; Y^1 and Y^2 are H; n is 1, 2 or 3 and m is 1, 2 or 3; reaction of a compound of formula (XII):

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(XII)

with a compound of formula (XIII)



(XIII)

5

wherein L is a displaceable group;

h) for compounds of formula (I) in which Z is HS-, by conversion of a thioacetate group in a corresponding compound;

and thereafter if necessary:

- 10 i) converting a compound of the formula (I) into another compound of the formula (I);
 ii) removing any protecting groups;
 iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester.

9. A method for producing an anti-cancer effect in a warm blooded animal which
 15 comprises administering to said animal an effective amount of a pyrimidine derivative of the formula (I) according to any one of claims 1 to 7, or a pharmaceutically acceptable salt, or *in vivo* hydrolysable ester thereof.

10. The use of a pyrimidine derivative of the formula (I) according to any one of claims 1
 20 to 7, or a pharmaceutically-acceptable salt, or *in vivo* hydrolysable ester thereof, in the manufacture of a medicament for use in the production of an anti-cancer effect in a warm blooded animal.

11. A pharmaceutical composition which comprises a pyrimidine derivative of the formula
 25 (I) according to any one of claims 1 to 7, or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof, and a pharmaceutically-acceptable diluent or carrier.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/01258

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D239/46 A61K31/505 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 15952 A (ZENECA) 15 June 1995 (1995-06-15) page 1 -page 36; claims -----	1-6,8, 10,11



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

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Date of the actual completion of the international search

20 July 2000

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 00/01258

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